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A Mathematical Model of the Opioid Epidemic in the State of Maine

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A MATHEMATICAL MODEL OF THE OPIOID EPIDEMIC IN THE STATE OF MAINE

by

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ABSTRACT

For the past two decades the United States has been embroiled in a prescription drug epidemic that has since grown in magnitude and complexity. The ripples of this epidemic have been especially apparent in the state of Maine, which has fought hard to mitigate the damage caused by addiction to pharmaceutical and illicit opioids. Using data from state and federal sources, we construct a mathematical model capturing the dynamics of the opioid epidemic in the state of Maine, specifically as it pertains to pharmaceutical opioids and heroin. Parameter fitting is performed followed by an uncertainty analysis to quantify potential error in parameter estimates. The model is analyzed to determine effective ways of controlling opioid abuse prevalence (both in the form of heroin and pharmaceutical opioid use) at different points in time, and stochastic simulations are run to test the effect of various control strategies on the number of opioid abusers in the system. These results are then presented with the hope of helping to inform public policy as to the most effective means of intervention.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

CHAPTER I

INTRODUCTION

As one of the most enduring and concerning public health crises to face the United States in the twenty-first century, the opioid epidemic has cemented itself as one of the greatest drug problems to face the country in its history. Since its beginning in the late 1990s, the opioid epidemic has taken the country by storm, affecting millions of Americans per year, and as recently as 2018 was killing more than a hundred Americans per day [13]. To understand how this happened, a synopsis of the epidemic and its origins is presented.

The National Institutes of Health provide the following as a definition of opioids: "Opioids are a class of drugs that act in the nervous system to produce feelings of pleasure and pain relief. Some opioids are legally prescribed by healthcare providers to manage severe and chronic pain. Commonly prescribed opioids include oxycodone, fentanyl, buprenorphine, methadone, oxymorphone, hydrocodone, codeine, and morphine. Some other opioids, such as heroin, are illegal drugs of abuse" [20]. Our discussion here will concern prescription opioids, while the use of illegal opioids will be discussed more completely in the paragraphs to follow.

Opioid analgesics as a treatment of pain in patients following surgery or trauma has been around long before federal legislation sought to extend the use of the same analgesics to treating noncancer pain [53]. The final decade of the twentieth century would see the most dramatic change in legislation regarding pain management. Some of the more compelling developments include The Joint Commission, a federal organization

in the U.S. that accredits health care institutions, compiling a list of pain standards in 1997 to guide policy surrounding pain management [27]. That same year, the Federation of State Medical Boards convened to set out suggested state guidelines for the use of controlled substances, most notably opioids, for the treatment of pain [44]. Two such consequences of this are easing regulatory strictness over opioid prescriptions and encouraging doctors to prescribe them more freely.

Adhering to the suggestions of the board, Maine would soon follow suit, passing Chapter 11 of the rules of the Board of Licensure in Medicine and the Board of Osteopathic Licensure. Adopted in 1999, the new rules set out pain treatment guidelines intended to reduce the reluctance of doctors in prescribing opioids for pain. These new guidelines also recognized pain treatment/relief as part of "quality medical practice" [83]. Although the law made it easier for doctors to prescribe opioids, the law specifically mentions that "inappropriate prescribing of controlled substances, including opioid analgesics, may lead to drug diversion and abuse by individuals who seek them for other than legitimate medical use."

Regardless of these warnings, opioid abuse would balloon in the years to follow. Kenan et al. [54] found that, from 2000-2009, the number of opioid prescriptions per 100 people in the United States increased by 35.2%. Opioid distribution by pharmacies, measured in milligrams per 100 persons, also more than doubled by 2010. Even the size of the individual prescriptions of common opioids such as oxycodone and hydrocodone increased by nearly 70% [54]. Prescriptions reached their peak at the end of the decade, when the national per capita prescription rate was 782 morphine milligram equivalents (MME) [50]. By comparison, the national per capita prescription rate in 1999 was 180 MME [70]. Maine would experience a similar trend, prescribing over 750 MME per capita both in 2006 and 2010, with over 14 per 100 people receiving a high dosage of over 90 MME per day for both years [77]. In 2010, Maine was among only 12 states in which this was the case.

The opioid prescription explosion was not without its consequences. From 1999-2010, mirroring the growth in opioid prescriptions, overdose deaths due to opioids grew steadily from a rate of less than 2 deaths per 100,000 people in 1999, to over double that in 2010 [23]. Although heroin and other synthetic opioids existed in 1999, their role in opioid overdose rates were vastly overshadowed by those attributed to prescription opioids. Once more, trends in Maine mirrored those on the national level, with drug overdose deaths involving opioids climbing from 1999 onward, until plateauing in 2005-06 [19]. It was around this time, no later than 2004, that the Maine legislature passed Section 7248 of Title 22: Health and Welfare, establishing the state's prescription monitoring program as a means of keeping records of dispensed controlled substances [1].

The FSMB would later update its model guidelines surrounding the regulation and use of controlled substances. In response to these updates, Maine repealed the Chapter 11 rules in favor of a joint rule, effective 2010, that was intended as an update to Maine laws surrounding the use of controlled substances for the treatment of pain. The new rule set, dubbed "Chapter 21: Use of Controlled Substances for Treatment of Pain," not only included an updated set of guidelines for the proper usage of controlled substances in the treatment of pain, but also included a set of suggestions for elements in a controlled substance contract, and a statement by the state boards involved on the treatment of pain [83].

In response to the growth in opioid prescriptions and the subsequent growth in pharmaceutical opioid overdoses, things began to change in 2010. Between 2010-11, a combination of national guidelines regulating the prescription of high-dose opioids and several studies linking high-dose opioids and risk of overdose provided ample incentive to limit high-dose opioid prescriptions across the country [32, 43, 51]. Beginning in 2011, Maine opioid prescriptions declined steadily [78]. From 2013-14, Maine opioid prescriptions decreased by 4.1%, which was 1.2% above the national average at the time

[78]. During this time, although prescriptions decreased, overdose deaths continued to increase as heroin use became more widespread. From 2010-14, heroin overdoses followed a similar trend as pharmaceutical opioid overdoses over a decade earlier. Within only a few years, the national heroin overdose death rate rose dramatically from under 1 death per 100,000 people to 4 deaths per 100,000 people in 2014 [23]. In Maine, although deaths due to pharmaceutical opioid overdoses began a steady decline (contrary to national trends during the same time period), heroin overdose deaths were on the rise [82]. In 2010, there were only 7 deaths in Maine involving heroin/morphine. By 2014, that number had increased more than eight-fold to 57 [42].

The most recent wave of the opioid epidemic began in 2013-14, when overdose deaths to the synthetic opioids tramadol and fentanyl surpassed overdose deaths to either heroin or pharmaceutical opioids [64]. From 2013-18, the national opioid overdose death rate involving synthetic opioids would climb dramatically from less than 2 deaths per 100,000 people to almost 10 deaths per 100,000 people. This trend was especially apparent in Maine. In 2013 there were only three overdose deaths involving nonpharmaceutical fentanyl/fentanyl analogues [42]. This number ballooned in subsequent years, to 43 in 2014, 87 in 2015, and eventually peaking in 2017 at 247 overdose deaths involving nonpharmaceutical fentanyl/fentanyl analogues [42].

A number of legislative changes were enacted to address the changing dynamic of the opioid epidemic in Maine. In 2015, Chapter 488 was passed, effective early 2016, which strengthened the prescription monitoring program [3]. Some key takeaways of this new law include limiting the MMEs per day a patient could receive and limiting the length of time that individuals could receive prescriptions for their treatment (with some exceptions of course, such as opioids for treating substance use disorders) [4, 63]. Also in 2015, Then-Governor Paul LePage held a summit in August to address the opioid epidemic in Maine. Following the summit, the Maine Opiate Collaborative was formed. The next year, in 2016, the collaborative released a report containing recommendations

for addressing the burgeoning problem [41]. The recommendations, summarized at the beginning of the report, are compartmentalized according to considerations of prevention and harm reduction, treatment, and law enforcement [41]. From 2015-16, more laws were passed at the state level addressing various parts of the opioid epidemic, including but not limited to Legislative Document (L.D.) No. 1537, L.D. No. 140, and L.D. No. 507 [21].

In 2017, Maine state Boards, including the Board of Licensure in Medicine, the State Board of Nursing, and the Board of Osteopathic Licensure, passed Chapter 21, effective 2018. Changes in the new law included some form of risk assessment before prescribing controlled substances for the treatment of pain, and advised the lowest dose possible be used for opiate-naive patients, to name a few (see [78]). Cogs were turning at the national level as well, when President Donald Trump declared the opioid epidemic a public health emergency in October that same year [6]. Since Governor Janet Mills has taken office in January of 2019, more has been done to further combat the severity of the opioid epidemic. Only a month after taking office, Governor Mills issued an executive order making anti-overdose drugs more widely available and training more recovery coaches, among other changes [11, 14].

Now, although state overdose deaths appear to be falling in recent years, Maine is still entangled in its war with opioid addiction. It is imperative that more work be done so that this decline continues into the following years, and the damages wrought by this epidemic are mitigated to the maximum extent achievable. Policymakers must be informed as to the best approaches in handling the continuing public health crisis. To assist in this effort, mathematical models can play an essential role in informing public policy as to the best intervention strategies. Deriving and analyzing a mathematical model of the opioid epidemic in Maine is the focus of this work.

Compartmental models, in which a population is subdivided into different compart-

ments or groups, have been used for a host of biological, ecological, and epidemiological queries [34, 68]. This formalism is not limited solely to problems of disease transmission, but any phenomenon in which the underlying dynamics involve the movement of a contagion between members in a community. Here, *contagion* need not be a literal microparasite, but an idea [31], a riot [33], or a noninfectious disease, such as drug abuse [25, 28, 62, 73, 84]. It is with this final category that we concern ourselves with primarily. Transmission and proliferation of drug abuse in a population occurs in a manner similar to that of diseases carried by microorganisms.

Several models of the opioid epidemic stand out in the literature, although their intents vary. In the case of [28], the focus is much more mathematical when compared to the work of Pitt et al. [73], with general observations gleaned from numerical sensitivity analysis. Battista et al. [28] found that, absent an addiction-free state, control efforts are best directed towards "reducing the average prescription length... and increasing the rate addicts enter treatment." The authors in [28] also seek to build on the results of White and Comiskey [84] by considering addiction to prescription drugs and the illicit use of leftover pharmaceuticals. On the other hand, Pitt et al. [73] place more emphasis on patient health in the context of a comparison of a variety of responses to the epidemic. Pitt et al. [73] found that the most beneficial approaches to opioid epidemic control were "policies that expand addiction treatment or directly mitigate harmful effects of addiction."

Aside from general opioid epidemic models incorporating both pharmaceutical and non-pharmaceutical opioids, there are also heroin epidemic models in the literature. This includes the efforts of Mackintosh and Stewart [62], which rely on a compartmental model of heroin addiction to suggest potential control policies, and Abdurahman et al. [25], who study a heroin epidemic model with time-delay. Other significant models in the literature include that of White and Comiskey [84], one of the first published mathematical models of opiate addiction.

The objective of the following work was to develop a deeper understanding of the opioid epidemic as it pertains to Maine, mathematically speaking, and extrapolate from this analysis pragmatic ways of mitigating its harmful effects. To the author's knowledge, this is the first mathematical model of the opioid epidemic to concern a particular state, and hopefully in this way acts as a stepping stone from which to guide other models in the future. In contrast to other opioid epidemic models in the literature, the scope of our analysis was the adult population of the state of Maine, so that data is not as difficult to obtain, and the results are more practical for our purposes. From a mathematical standpoint, we employed a novel compartmentalization in which individuals abusing opioids are divided into a pharmaceutical compartment and a nonpharmaceutical (heroin) compartment.

The structure of this thesis is presented as follows: some preliminary information is given in Chapter II, including background theory for ordinary differential equations and infectious disease modeling. The mathematical model of the opioid epidemic in Maine is formulated in Chapter III. In Chapter IV we analyze model behavior and forecasts. Finally, Chapter V discusses the results of the analysis carried out in Chapter IV and concludes with some directions for future work.

CHAPTER II

BACKGROUND

Some necessary preliminary concepts are presented in the following section. Many of the concepts related to dynamical systems are taken from [71].

ODE Theory

To understand the mathematical terms and results presented in this paper, a fundamental understanding of ordinary differential equation (ODE) theory is required. An ordinary differential equation shall be denoted as

$$\dot{x} = f(x), \tag{1}$$

where $\dot{x}$ denotes the derivative of $x = (x_1, \ldots, x_n)$ with respect to time t (the independent variable), and $f(x) = (f_1(x), \ldots, f_n(x))$ is a function depending only on the dependent variable x. It is because of this property that $f(x)$ is referred to as an *autonomous* ODE. The derivative of x with respect to time is simply the rate that x changes with respect to time. Combined with an initial condition on x at $t = 0$, which we denote by x_0, we get the following initial value problem (IVP):

$$\begin{aligned} \dot{x} &= f(x) \\ x(0) &= x_0. \end{aligned} \tag{2}$$

On some domain D, a function $g(x)$ is C^1, written as $g \in C^1(D)$, if $g'(x)$ exists and is continuous for all $x \in D$. If the system $f(x)$ in (2) is C^1 on its domain, then a solution of the system, which we denote by $u(t)$, is a C^1 function on some time interval T containing $t = 0$ satisfying $\dot{u} = f(u)$ for all $t \in T$, and is such that $u(0) = x_0$. However, how do we know such a solution exists? Furthermore, is such a solution unique? These questions are answered by the following theorem, taken from [71]:

Theorem 2.1 (The Fundamental Uniqueness-Existence Theorem)**.** *Let E be an open subset of $\mathbb{R}^n$ containing x_0 and assume that $f \in C^1(E)$. Then there exists an $a > 0$ such that the IVP in* (2) *has a unique solution $u(t)$ on the interval $[-a, a]$.*

We forego a proof of this theorem, as the scope is beyond that of this paper. Regarding the language used in the theorem, an open set can roughly be described as a generalization of an open interval. For example, $(0,1)$ is an open interval on the real line, which is the set of all $x \in \mathbb{R}$ such that $0 < x < 1$. The final phrase in the above theorem can be restated as "... has a unique solution $u(t)$ for $-a \leq t \leq a$". What exactly do we know about the constant a? The above theorem stipulates that $a > 0$, but it gives no manner as to how large, or small, a may be. Thus, this theorem establishes *local* existence of a solution, but there is no guarantee such a solution exists for all $t > 0$. A stronger claim of existence is referred to as *global* existence, but this is in general rather difficult to prove, and is a luxury enjoyed by linear systems (of which our model is not).

A simple example should help to illustrate the concepts presented above. Consider a population (P) of organisms. Suppose that each organism in this population reproduces at a rate of b per unit time, and dies at a rate of μ per unit time. During some very small interval of time, we expect $bP\Delta t$ new offspring and $\mu P\Delta t$ dead organisms. Together, this means that the change in P, denoted ΔP, over some short interval of time is $\Delta P = bP\Delta t - \mu P\Delta t = (b-\mu)P\Delta t$. Dividing either side by Δt and taking the limit $\Delta t \to 0$, we arrive at the simple ODE $\dot{P} = (b-\mu)P$ to model this population. Suppose further

that at time $t_0 = 0$, the population is of size $P(0) = N$, then the population satisfies the IVP

$$\begin{aligned} \dot{P} &= (b-\mu)P \\ P(0) &= N. \end{aligned} \tag{3}$$

This ODE is linear and also separable, so that a solution can be found as follows:

$$\dot{P} = \frac{dP}{dt} = (b-\mu)P \implies \frac{dP}{P} = (b-\mu)\,dt \implies \int \frac{1}{P}\,dP = \int (b-\mu)\,dt.$$

Evaluating the integrals together with the initial condition yields the solution

$$P(t) = Ne^{(b-\mu)t}.$$

Note that in this expression, if $b < \mu$ then $P(t) \to 0$ as $t \to \infty$, and when $b > \mu$ then $P(t) \to \infty$ as $t \to \infty$. This agrees with the physical notions of a population going extinct and a population growing exponentially, respectively. This linear example behaves rather nicely but, in the case of nonlinear ODEs, closed-form solutions cannot always be found analytically and so we must rely on other tools to perform a meaningful analysis.

At one point we will refer to our model as *well-posed* within some domain. It is important that our model is well-posed, as an ill-posed mathematical model can produce nonphysical behavior and is therefore not a good model for a physical problem. Typically, a system is well-posed if (i) a solution exists, (ii) that solution is unique, and (iii) the behavior of the system changes continuously with respect to initial conditions. (i)-(ii) are established by the theorem above, but what of the final point, and what does this mean? We begin by citing the following theorem from [71]:

Theorem 2.2 (Dependence on Initial Conditions)**.** *Let E be an open subset of $\mathbb{R}^n$ containing x_0 and assume that $f \in C^1(E)$. Then there exists an $a > 0$ and a $\delta > 0$ such that*

for all $c \in N_\delta(x_0)$ *the IVP*

$$\dot{x} = f(x)$$
$$x(0) = c$$

where c *is a parameter, has a unique solution* $u(t,c)$ *with* $u \in C^1(G)$ *where* $G = [-a,a] \times N_\delta(x_0) \subset \mathbb{R}^{n+1}$.

Here, $N_\delta(x_0)$ refers to a neighborhood around x. Specifically, $N_\delta(x_0)$ is a region of points in $\mathbb{R}^n$ within some Euclidean distance of x_0. Roughly, this theorem states that if we perturb the initial conditions of our IVP slightly, then a solution of this new system exists and is unique. Even further, this new solution depends continuously (actually C^1) on changes in initial condition near x_0. Thus, this makes our system well-posed. We will revisit this theorem in a later subsection to establish some local sensitivity results.

We are also interested in the equilibria of the ODE systems we work with. An equilibrium x^* of the ODE in (1) is such that $f(x^*) = 0$, since then $u(t) = x^*$ is a solution of the ODE. Mathematically, equilibria are where a system does not change with respect to time. This is significant biologically speaking in the context of disease modeling, because an equilibrium indicates that either the disease has died off (referred to as the *disease-free equilibrium*, or DFE), or the disease is unchanging within the population (the *endemic* equilibrium). The *stability* of these equilibria dictates the overall behavior of solutions, and hence the long-term qualitative behavior of the ODE system. Stability in this case means that the solutions of our system do not change much under small perturbations. An equilibrium point is either stable or unstable; the former indicating that a solution of (1) near an equilibrium point x^* will remain near x^* as $t \to \infty$, and the latter characterizes the opposite situation, in which a solution of (1) near x^* will tend to move away from x^* in forward time.

In the case of nonlinear systems, stability of equilibria can be determined by the eigenvalues of the Jacobian of $f(x)$ evaluated at x^*, which we write as $Df(x^*)$. The Jacobian of (1) is

$$Df(x) = \begin{pmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \cdots & \frac{\partial f_1}{x_n} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \cdots & \frac{\partial f_2}{\partial x_n} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{\partial f_n}{\partial x_1} & \frac{\partial f_n}{\partial x_2} & \cdots & \frac{\partial f_n}{\partial x_n} \end{pmatrix}.$$

This is established by the Hartman-Grobman theorem, which states that the behavior of a solution of (1) near a hyperbolic equilibrium is well-approximated by the linearization of $x' = f(x)$ at that equilibrium, given by $z' = f'(x^*)z = Df(x^*)z$. We ignore cases when the real part of any eigenvalues are 0, so we only consider equilibria that are referred to as *hyperbolic*. The stability and respective criteria for each situation considered is given below (taken from [71]):

1. x^* is a *sink* if the real part of all eigenvalues of $Df(x^*)$ are less than 0. In this case, solutions of (2) starting close to x^* converge to x^* as $t \to \infty$. x^* is thus asymptotically stable.

2. x^* is a *source* if the real part of all eigenvalues of $Df(x^*)$ are greater than 0. The opposite of the previous case occurs, in which solutions of (2) starting near x^* are repulsed by x^* in forward time, and so x^* is unstable.

3. x^* is a *saddle* if the the real part of at least one eigenvalue of $Df(x^*)$ is positive, and if the real part of at least one eigenvalue of $Df(x^*y)$ is negative. In this case, x^* is a semi-stable equilibrium point, characterized as having both unstable and asymptotically stable solutions.

To illustrate these concepts, we provide an example. Consider the logistic equation with

growth rate r and carrying capacity $K > 0$, given by

$$x' = f(x) = rx\left(1 - \frac{x}{K}\right)$$

where x is a population of organisms. The rate of change of the population $f(x)$ vanishes for $x = 0$ and $x = K$, representing the events of extinction and reaching the carrying capacity of the habitat, respectively. To characterize the equilibria of f, we calculate the derivative as follows:

$$f'(x) = r\left(1 - \frac{2x}{K}\right).$$

The stability of the equilibria can be determined by evaluation of this derivative at the equilibria found above. For $x = 0$, the derivative is $f'(0) = r$. If $r < 0$, or the growth rate is negative, then this equilibrium point is asymptotically stable, and the population in the system will eventually go extinct. If $r > 0$, or the growth rate is instead positive, then this equilibrium point is unstable, and populations will not go extinct. For the second equilibrium point found, $f'(K) = -r$. The sign change indicates that the equilibrium point at $x = K$ will have the stability opposite that of the equilibrium point at $x = 0$. That is, when $x = 0$ is asymptotically stable, $x = K$ will be unstable, as populations will tend to extinction rather than to the carrying capacity of the environment. Similarly, when $x = 0$ is unstable, then $x = K$ is asymptotically stable and all populations will tend toward the carrying capacity K.

Parametric Uncertainty and Sensitivity Analysis

Many dynamics behind the opioid epidemic are unclear, and in some instances the necessary data is not available from which to derive parameter estimates. In such instances, it becomes necessary to fit the model to the data that is available and, through a process of optimization, arrive at a best guess that minimizes the error between model and data.

This process, referred to as parameter fitting, can be used to approximate unknown parameters. A common method by which this is accomplished is called the least-squares method. Suppose we have a set of q parameters $\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_q)$, and m data points given by $y_1, y_2, \ldots, y_m$ that correspond to the state of the system at times $t_1, t_2, \ldots, t_m$. Consider the IVP given by

$$\begin{aligned} \dot{x} &= f(x, \boldsymbol{\theta}), \\ x(0) &= c, \end{aligned} \tag{4}$$

and let $u(t_j, \boldsymbol{\theta})$, for $j \in \{1, 2, \ldots, m\}$, denote the solution of (4) with parameters $\boldsymbol{\theta}$ evaluated at t_j. The *residual* of a model at some data point y_j is the difference between the prediction of the model and the actual data, or $y_j - u(t_j, \boldsymbol{\theta})$ for some j. The least-squares method determines the optimal parameter values $\boldsymbol{\theta}$ that minimize the sum of the squared residuals:

$$\sum_{j=1}^{m} \big(y_j - u(t_j, \boldsymbol{\theta})\big)^2.$$

The least-squares method can be implemented in MATLAB using the native function lsqcurvefit.

Once parameters are determined, how can we quantify the potential error in our estimates? Parameter uncertainty is useful for quantifying uncertainty in parameter values introduced by either a scarcity of data or from the method utilized to arrive at the estimates in the first place. Our method for quantifying parameter uncertainty, taken from [38], is presented in the corresponding subsection in Chapter IV.

There is also the question of how sensitive the variables x are to the model parameters, $\boldsymbol{\theta}$. The sensitivity, in this context, can be measured by changes in x in response to small perturbations to θ_i for some $i \in \{1, 2, \ldots, q\}$. Consider the parametric IVP

$$\begin{aligned} \dot{x} &= f(x, \boldsymbol{\theta}) \\ x(0) &= x_0 \end{aligned} \tag{5}$$

where $\boldsymbol{\theta} = (\theta_1, \theta_2, \ldots, \theta_q) \in \mathbb{R}^q$ is a parameter vector, and $x_0 \in \mathbb{R}^n$ is the (fixed) initial condition. Sensitivities of the state variables of (5) with respect to parameters are given in the following theorem, which is an adjusted version of a result presented in Section 3.3 of [56]. The proof of this well-known result uses a transformation and then applies Theorem 2.2.

Theorem 2.3. *Let E be an open subset of $\mathbb{R}^{n+q}$ containing $(x_0, \boldsymbol{\theta}_0)$ and assume that $f \in C^1(E)$. Then there exists an $a > 0$ and a $\delta > 0$ such that there is a unique solution $u(t, \boldsymbol{\theta})$ of the IVP in (5) with $u \in C^1(G)$ where $G = [-a, a] \times N_\delta(\boldsymbol{\theta}_0)$. Moreover,*

$$\Phi(t) = \frac{\partial u}{\partial \boldsymbol{\theta}}(t, \boldsymbol{\theta}_0)$$

is the unique solution of the sensitivity system

$$\begin{aligned} \dot{\Phi}(t) &= \frac{\partial f}{\partial x}(u(t, \boldsymbol{\theta}_0), \boldsymbol{\theta}_0)\, \Phi(t) + \frac{\partial f}{\partial \theta}(u(t, \boldsymbol{\theta}_0), \boldsymbol{\theta}_0) \\ \Phi(0) &= 0 \end{aligned} \tag{6}$$

on the interval $[-a, a]$.

Proof: We first show that such a solution, denoted u, exists on some interval and is unique. Let $y = (x, \theta)$ and consider the *extended* system given by $\dot{y} = h(y)$, where

$$h(y) = \begin{pmatrix} f(y) \\ 0 \end{pmatrix} = \begin{pmatrix} f(x, \theta) \\ 0 \end{pmatrix}.$$

This system becomes an IVP with initial value given by $y(0) = c = (x_0, \theta)$. Since f is C^1 on E, it holds that h is C^1 on E as well. By Theorem 2.1.2, there exists an $a > 0$ and a

$\delta > 0$ such that for all $c \in N_\delta(c_0)$, where $c_0 = (x_0, \theta_0)$, the IVP

$$\begin{aligned} \dot{y} &= h(y) \\ y(0) &= c \end{aligned} \tag{7}$$

has a unique solution $u(t,c)$ with $u \in C^1(G)$, where $G = [-a,a] \times N_\delta(c_0)$. To prove the second part of the theorem, we use the result of the corollary in Section 2.3 of [71], which states that

$$\Phi(t) = \frac{\partial u}{\partial c}(t, c_0),$$

is the solution of the IVP

$$\begin{aligned} \dot{\Phi} &= Dh[u(t,c_0)]\Phi \\ \Phi(0) &= I \end{aligned} \tag{8}$$

for $t \in [-a,a]$. We first expand Φ in block matrix form to obtain

$$\Phi(t) = \frac{\partial u}{\partial c}(t,c) = \begin{pmatrix} \frac{\partial x}{\partial c} \\ \frac{\partial \theta}{\partial c} \end{pmatrix} = \begin{pmatrix} \frac{\partial x}{\partial x_0} & \frac{\partial x}{\partial \theta} \\ 0 & I \end{pmatrix},$$

where I is the identity matrix. Evaluating the product $Dh[u(t,c)]\Phi$ in block matrix form yields

$$Dh[u(t,c)]\Phi = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial \theta} \\ 0 & 0 \end{pmatrix} \Phi = \begin{pmatrix} \frac{\partial f}{\partial x} & \frac{\partial f}{\partial \theta} \\ 0 & 0 \end{pmatrix} \begin{pmatrix} \frac{\partial x}{\partial x_0} & \frac{\partial x}{\partial \theta} \\ 0 & I \end{pmatrix} = \begin{pmatrix} 0 & \frac{\partial f}{\partial x}\frac{\partial x}{\partial \theta} + \frac{\partial f}{\partial \theta} \\ 0 & 0 \end{pmatrix}.$$

Note that

$$\frac{\partial f}{\partial x}\frac{\partial x}{\partial x_0} = 0$$

as we are assuming the initial condition x_0 to be constant (we are only concerned with

changes to our parameter values θ). Our final system becomes

$$\frac{d}{dt}\begin{pmatrix} \frac{\partial x}{\partial x_0} & \frac{\partial x}{\partial \theta} \\ 0 & I \end{pmatrix} = \begin{pmatrix} 0 & \frac{\partial f}{\partial x}\frac{\partial x}{\partial \theta} + \frac{\partial f}{\partial \theta} \\ 0 & 0 \end{pmatrix}. \tag{9}$$

Hence, we have that

$$\hat{\Phi}(t) = \frac{\partial x}{\partial \theta}(t, \theta_0)$$

satisfies the IVP given by

$$\begin{aligned} \dot{\hat{\Phi}}(t) &= \frac{\partial f}{\partial x}(x(t,\theta_0),\theta_0)\hat{\Phi}(t) + \frac{\partial f}{\partial \theta}(x(t,\theta_0),\theta_0) \\ \hat{\Phi}(0) &= 0 \end{aligned} \tag{10}$$

for $t \in [-a, a]$ and $\theta \in N_\delta(\theta_0)$. The IVP is obtained in (9), and the conditions on t and θ are directly inherited from the properties of Φ. The initial condition is found by evaluating

$$\hat{\Phi}(0) = \frac{\partial x}{\partial \theta}(0, \theta_0) = \frac{\partial}{\partial \theta}(x_0) = 0.$$

□

To illustrate the sensitivity system in the above theorem, we refer back to our system in (3). Our system in this case is the ODE given by $f(P) = \dot{P} = (b-\mu)P$. We are interested in how small perturbations to the parameter vector $\theta = (b, \mu)$ affect the state variable P. The corresponding IVP in (6) in this case becomes

$$\begin{aligned} \dot{\Phi}(t) &= \frac{\partial f}{\partial P}(x(t,\theta_0),\theta_0)\Phi(t) + \frac{\partial f}{\partial \theta}(x(t,\theta_0),\theta_0) \\ &= (b_0-\mu_0)\Phi(t) + \begin{pmatrix} P(t,\theta_0) & -P(t,\theta_0) \end{pmatrix} \\ \Phi(0) &= \begin{pmatrix} 0 & 0 \end{pmatrix} \end{aligned} \tag{11}$$

The sensitivity systems with respect to b and μ are then

$$\frac{\partial \dot{P}}{\partial b} = (b_0 - \mu_0)\frac{\partial P}{\partial b} + P$$

and

$$\frac{\partial \dot{P}}{\partial \mu} = (b_0 - \mu_0)\frac{\partial P}{\partial \mu} - P,$$

respectively. Let $b_0 = \mu_0 = 1$, implying $P = Ne^{(b_0-\mu_0)t} = N$. Let $P_b = \partial P/\partial b$ and similarly define P_μ. Then the first sensitivity equation gives $P_b = Nt + C$. To solve for C we assume that $P_b(t = 0) = 0$, which implies that $C = 0$. Thus, the sensitivity of the variable P to the birth rate b is given by the function $P_b = Nt$. Similarly, assuming the initial condition $P_\mu(0) = 0$, we can show that $P_\mu = -Nt$. We can compare these solutions to those we would have obtained by taking the partial derivatives directly. In the former case of the sensitivity of P to the variable b, we have

$$\frac{\partial P}{\partial b} = \frac{\partial}{\partial b}\left(Ne^{(b-\mu)t}\right) = Nte^{(b-\mu)t}.$$

Using the parameter values $b_0 = \mu_0 = 1$, we arrive at the solution derived above, and similarly for the case of $\partial P/\partial \mu$.

In some instances, however, we are not only interested in the sensitivity of model output to small perturbations, but parameter values that are free to change within a range of possible values that need not be small. This *global sensitivity analysis* is much better in determining deeper interactions between parameters in the model that are not made apparent in an otherwise local analysis.

For global sensitivity analysis, we employ the elementary effects method. The elementary effects method was initially presented by Morris [65] as a screening procedure to identify influential parameters in a computationally expensive model, with results comparable to other sensitivity analysis methods [75, 85]. The elementary effects method

is attractive due to its simplicity and intuitive nature. We present the method here and apply it in Chapter IV. Consider a mathematical model f with n input factors. Let Y denote some model output, so that we have

$$Y = f(x_1, x_2, \ldots, x_n).$$

Each x_i is assumed to take on an integer value in $1 \leq x_i \leq p-1$ for some p, as done in [36], regardless of the "true" value of the model factor x_i. Each x_i possesses a range of possible values, the lower bound of which we denote by x_i^L and the upper bound of which we denote by x_i^U. Here, x_i^L and x_i^U need not be integers, but are instead the lower and upper bounds respectively of the range of possible values we will consider in the analysis of x_i. The product of all such ranges we refer to as the region of experimentation, denoted by Ω. That is,

$$\Omega = [x_1^L, x_1^U] \times [x_2^L, x_2^U] \times \cdots \times [x_n^L, x_n^U] \subset \mathbb{R}^n.$$

The *elementary effect of* x_j, for $1 \leq j \leq n$, can be found by first changing x_j by a value Δ, where Δ is a predetermined value in $\{1, 2, \ldots, p-1\}$. This adjusted value of x_j is then scaled to fall within its respective factor range as follows:

$$x_j^L + (x_j + \Delta)(x_j^U - x_j^L)(p-1).$$

The sign of Δ depends on whether the adjusted value of x_j remains in the range $[x_j^L, x_j^U]$ after scaling. If both $x_j + \Delta$ and $x_j - \Delta$ fall within this range after scaling, then the choice can be made arbitrarily. We denote this scaled value of $x_j + \Delta$ as $y_{j,\Delta}$, and note that $y_{j,\Delta} \in [x_j^L, x_j^U]$. We scale the remaining x_i such that they fall within their respective factor ranges as well, and denote these scaled factors by y_i. The elementary effect of

x_j, for $1 \leq j \leq n$ and denoted $ee(x_j)$, is

$$ee(x_j) = \frac{f(y_1, y_2, \ldots, y_{j,\Delta}, \ldots, y_n) - f(y_1, y_2, \ldots, y_j, \ldots, y_n)}{\Delta}.$$

This process is repeated r times, referred to as the number of *trajectories*, where r depends on the size and complexity of the region of experimentation. That is, the analysis of a larger number of factors should be accommodated by a larger number of trajectories.

Multiple measurements of the elementary effects of x_i must be made, at which point they are then averaged and the standard deviation calculated for analysis. The average of the elementary effects of a single factor is denoted by μ, while the standard deviation of the elementary effects of a factor is denoted by σ. The purpose of the mean is to quantify the overall effect that x_i has on the output Y, while σ gives the "spread" of the elementary effects, quantifying dependency on inputs/other factors and is generally used to elucidate any nonlinear behavior between parameters [65]. A small σ corresponds to linear parametric behavior in relation to other model factors, whereas a large σ is indicative of nonlinearity or coupled interactions with other parameters. Specifically, "A large measure of spread indicates an input whose influence is highly dependent on the values of the inputs - that is, one involved in interactions or whose effect is nonlinear" [65]. Additionally, we also record the average of the absolute values of the elementary effects of the various factors, denoted by μ^*. This consideration, attributed to [35], ignores the potential "canceling" of positive and negative elementary effects. A large value of μ^* indicates an influential parameter, while a small value of μ^* suggests an insignificant or even negligible parameter.

Disease Modeling

The idea of compartmental models to model disease first originated with the work of W.O. Kermack and A.G. McKendrick [55]. Their theory and model, aptly dubbed the Kermack-McKendrick model, would lay the groundwork for the eventual development of the susceptible-infected-recovered (SIR) model, shown below.

$$\begin{aligned} \dot{S} &= -\beta S \frac{I}{N} \\ \dot{I} &= \beta S \frac{I}{N} - \gamma I \\ \dot{R} &= \gamma I. \end{aligned} \tag{12}$$

As the name implies, this mathematical model quantifies interactions between susceptible (S), infected (I), and recovered (R) individuals. It should be noted that these classifications are disjoint, and such a *compartmentalization*, or organization of the population into disjoint categories, is a standard feature of modern disease models. In regards to the system shown above, β is the contact rate adequate for transmission, γ is the recovery rate, and N is the total population, or $N = S + I + R$. The force of infection, in this context, is just the number of contacts an individual makes, multiplied by the probability of transmission per contact. For example, in a system where individuals on average make 2 contacts per day and disease transmission is successful in 40% of contacts with an infected individual, the transmission rate is $\beta = 2 \times 0.4 = 0.8$. The recovery term is more readily understood. Continuing with our hypothetical example, suppose that infected individuals remain infectious on average for a week. The recovery rate is then $1/7 \approx 0.143$ day^{-1}. The reason for this is that one can show that recovery times follow an exponential distribution with mean $1/\gamma$. However, we forego this discussion and instead refer the reader to Section 9.2 of [34].

There are several assumptions about this model that deserve further elaboration:

I An individual is assumed equally likely to contact any other individual in the population. This is referred to as *homogeneous mixing*.

II Disease transmission is assumed proportional to the number of infected individuals in the system. This is referred to as *standard incidence*, or frequency-dependent transmission.

III The population of the system is constant.

From I and II above, the rate of successful transmission after contact with an infected individual is $\beta(I/N)$. The number of newly infected susceptible individuals is then given by $\beta S(I/N)$. III can be realized by the following observation:

$$\frac{dN}{dt} = \frac{dS}{dt} + \frac{dI}{dt} + \frac{dR}{dt} = 0.$$

Since $dN/dt = 0$, the population remains constant. This assumption is common when, for reasons of the time scale or the size of N, considerations of a dynamic population (e.g. immigration or death) are negligible.

Also important to mention in the context of disease models is the quantification of equilibria and their respective stabilities. This was discussed previously in general, but in epidemiological models equilibria stability can determine the direction of the epidemic. In such situations it is useful to derive the *reproduction number*, denoted R_0, of the system. The reproduction number is the average number of infected individuals generated by a single infected person in a completely non-immune population. If equilibria of the disease model exists, then it is typically the case that the DFE is asymptotically stable when $R_0 < 1$, and the EE is asymptotically stable when $R_0 > 1$.

Extending the mathematics outlined above to the opioid epidemic may seem unintuitive, as social contagions behave much differently than agents of disease. However, as the fundamental dynamics remain the same (i.e. there is a mode of susceptibility,

transmission, and recovery), such a framework can indeed work in the context of the transmission of behaviors rather than microorganisms. We rely on much of the same assumptions as above for simplicity, with several changes, which we introduce in the next section alongside our model.

CHAPTER III

A DYNAMIC MODEL OF THE OPIOID EPIDEMIC IN MAINE

Model Formulation

We first introduce our model and then discuss challenges and previous model iterations. The model schematic is shown in Figure 1.

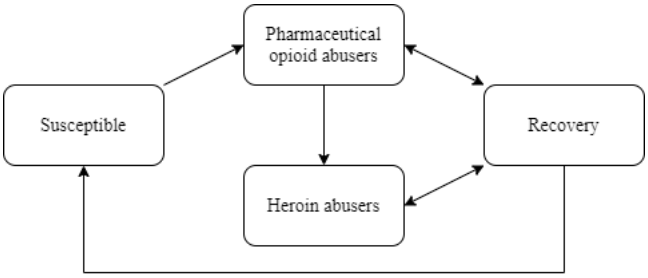


Figure 1: Schematic of our opioid epidemic model.

The scope of our model is Maine adults (age 18+). The population is compartmentalized into four categories. These compartments are susceptible (S), addicted to pharmaceutical opioids (A_P), addicted to heroin (A_H), and in rehabilitation/treatment (R). We let $N = S + A_P + A_H + R$ denote the entire adult population. Regarding our use of the word "addiction," this refers to individuals with a substance use disorder. Thus, our definitions of A_P and A_H could be restated as individuals with (pharmaceutical) opioid use disorder (POUD) and individuals with heroin use disorder (HUD), respectively. Note that the definition of A_P does not rely on the source of the pharmaceutical opioids, e.g. whether the opioids are diverted (i.e. “the unlawful channeling of regulated pharmaceuticals from legal sources to the illicit marketplace” [52]) or obtained via prescription.

The model operates on a number of key assumptions similar to those discussed above, which are as follows:

1. The population mixes homogeneously.
2. The only considered mechanism of developing heroin addiction assumes that the individual first abused prescription opioids.
3. Effects of individuals leaving the population for reasons besides death are ignored.
4. Individuals re-entering the compartments A_H and A_P as a result of failed treatment are assumed to do so at a rate proportional to the overall addicted population.
5. Entry into the system is assumed equivalent to the birth rate in the state of Maine.
6. Individuals were not assumed to move from A_H to A_P.
7. Nonlinear interactions resulting in transmission are assumed to only matter in the movement of individuals from A_P to A_H.

Assumption 1 above follows from typical mathematical assumptions for modeling disease spread (see the third subsection in Chapter II). Regarding Assumption 2, research indicates that the majority of individuals abusing heroin first began misusing pharmaceutical opioids [40]. Church et al. [39] state that "95 percent of interview respondents used prescription opioids before initiating heroin." Furthermore, Lankenau et al. [59] found that, in a sample of 50 heroin users from 2008-09, 86% “initiated opioid misuse prior to heroin.” Beyond this, other nonlinear routes of movement into A_H dictated by interactions between the susceptible and recovered compartments and individuals in A_H were considered, but parameter fitting revealed the inclusion of these nonlinear routes of transmission was negligible. This is explained more fully in the following subsections. The only nonlinear route into A_H that parameter fitting revealed to be significant

was interactions between individuals of A_P and A_H. Thus, the only individuals entering A_H must have once been in A_P, or have already abused pharmaceutical opioids.

Assumption 3 was made given Maine's relatively steady adult population in recent years and the relatively small time window of analysis we consider. Assumption 4 was made to compensate for a lack of data studying the abuse patterns of individuals failing rehabilitation. In place of a more complicated mechanism of re-entry, a simple proportionality assumption was made. That is, as the number of heroin abusers in the system increases, this will be reflected in a greater number of individuals transitioning from R to A_H after treatment has failed. Re-entry into A_P from R follows a similar mechanism.

A dynamic population is largely ignored, save for a natural death rate and deaths attributed to overdoses. That being the case, the birth rate was assumed equivalent to the rate of entry into the system, as in Assumption 5. Regarding Assumption 6, individuals can move from pharmaceutical opioid abuse to heroin abuse, but the reverse direction is not considered. This was mainly to simplify overall dynamics and because the necessary data to include such a mechanism is lacking. Finally, Assumption 7 simply means that the only nonlinear term of transmission is the $\beta A_P(A_H/N)$ term controlling movement from A_P to A_H. This is in contrast with such models as [28] and [84]. The reasons for making this assumption are discussed in the Parameter Fitting subsection. Incorporating these assumptions into a deterministic model yields the following system of ODEs:

$$\begin{aligned}
\dot{S} &= bN - \varepsilon_P \rho S + \tau(1-\delta)R - \mu S \\
\dot{A}_P &= \varepsilon_P \rho S - \gamma A_P - \eta_P A_P - \beta A_P \frac{A_H}{N} + \tau\delta R\left(\frac{A_P}{A_P + A_H}\right) - (\mu + \mu_P)A_P \\
\dot{A}_H &= \gamma A_P - \eta_H A_H + \beta A_P \frac{A_H}{N} + \tau\delta R\left(\frac{A_H}{A_P + A_H}\right) - (\mu + \mu_H)A_H \\
\dot{R} &= \eta_P A_P + \eta_H A_H - \tau R - \mu R.
\end{aligned} \tag{13}$$

A table of the parameters and their respective meanings are given in Table 1. Individuals

Parameter	Description	Source	Value	Range
b	Birth rate	[10]	0.0117	0.00585-0.0234
β	Transmission rate b/w A_P and A_H	Fit	13.286	12.656-13.916
γ	Transition rate from A_P to A_H	Fit	0.1219	0.118-0.1257
ε_P	Rate of POUD development from prescription	[28]	0.00744	0.00372-0.01488
ρ	Proportion of Maine adults w/prescriptions	[72]	0.2	0.1-0.3
μ	Age-adjusted death rate	[57, 66, 67, 86, 87]	0.00728	0.00364-0.01456
τ	Treatment completion rate	Fit	1.125	1.124-1.126
η_P	Rate of entering treatment for POUD	[2, 5, 7, 9, 15]	0.2518	0.09823-0.4054
η_H	Rate of entering treatment for HUD	[2, 5, 7, 9, 15]	0.5379	0.4351-0.6407
μ_P	Overdose rate for POUD	[82]	0.009383	0.00591-0.01286
μ_H	Overdose rate for HUD	[82]	0.01451	0.008675-0.02035
δ	Relapse probability	[28]	0.9	0.8-1.0

Table 1: Parameter names, descriptions, sources, and values for the baseline model. Parameter ranges are also provided. Where possible, parameter ranges are the respective 95% confidence intervals.

enter the system at a rate of b, which is simply the average birth rate of the state of Maine for the years 2014-2018 [18], and die at an annual rate of μ. The age-adjusted death rate, μ, is the average national age-adjusted death rate for the five years we have data for (2014-2018) [57, 66, 67, 86, 87].

Adults with an opioid prescription become addicted to pharmaceutical opioids at an annual rate of ε_P, at which point they move into the A_P compartment. The proportion of Maine adults with an opioid prescription is given by the parameter ρ. This proportion was difficult to ascertain, as information on prescription information is not publicly available, and must be obtained from the Maine Prescription Monitoring Program. A

report in the state of Maine done in 2014 found that 21.9% of the population were prescribed opioids [72]. Since this includes individuals younger than 18 years of age (and thus outside the scope of our model), the proportion was assumed constant at 20% of the adult population.

Individuals can move from A_P to A_H by either a linear or nonlinear process. The linear rate, given by γ, is simply the rate at which individuals progress to heroin use following misuse of prescription drugs [49]. The nonlinear process is given by the force of infection term $\beta(A_H/N)$, which explicitly accounts for a transition in drug abuse as a result of contact with heroin abusers. The parameter β was one of three that were determined via parameter fitting (see Chapter III).

Pharmaceutical opioid abusers seek treatment at a rate of η_P and die due to overdose at a rate of μ_P. Similarly, heroin abusers seek treatment at a rate of η_H and die due to overdose at a rate of μ_H. Individuals complete treatment at a rate of τ, in which case individuals relapse with probability δ. Regarding relapse, we assumed that the state average did not deviate significantly from the value used in [28]. Following relapse, the individual will enter A_P and A_H at a rate proportional to the number of pharmaceutical opioid abusers and heroin abusers, respectively, in the system. If treatment is successful, recovered individuals re-enter the susceptible compartment.

Model construction was difficult for a variety of reasons, most notably data limitations. The model went through several iterations, which we elaborate on here. The first modeling attempt centered around differentiating between abusers of pharmaceutical opioids (i.e. prescription opioids, obtained either via prescription or community diversion) and nonpharmaceutical (or 'illicit') opioids, such as heroin and illicit fentanyl. Immediately, the issue arose of how to handle individuals abusing multiple opioids at the same time, complicating the typical disjoint compartmentalization assumed in disease models. The solution to this problem was to provide for a separate compartment to which

individuals abusing both pharmaceutical and nonpharmaceutical opioids would belong. Another unique feature of the original model was that, prior to addiction, susceptible individuals belonged to compartments defined by risk. That is, individuals were either classified as low-risk or high-risk to developing addiction. The reason for making such a distinction was because individuals developing addiction to pharmaceutical opioids occurred via a different process and at different rates than individuals developing addiction to nonpharmaceutical opioids. A distinction based on predictor classification seemed to most accommodate these differences. Of course, there was also a recovery compartment for individuals in treatment for drug abuse. A schematic of this first iteration is given in Figure 2.

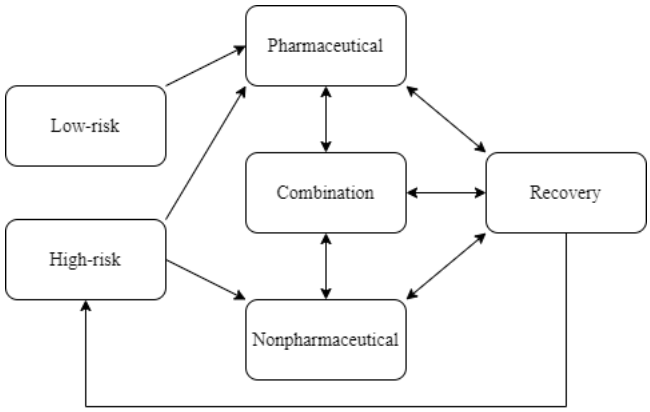


Figure 2: Schematic of the original opioid epidemic model, where the susceptible population is split into low- and high-risk categories and the addicted population is split into categories depending on the nature of the drug abuse disorder.

Eventually, it was decided that this model was not practical, as there were many transitions requiring more data than what is currently available in order to quantify, and so a simpler model construction was favored. Some notable changes between this first model and subsequent versions include (1) omitting the risk classification of susceptible individuals, (2) omitting the "combination" compartment (that is, consideration of the population abusing multiple opioids at once), and (3) limiting the scope of the nonpharmaceutical opioids compartment to only heroin. Regarding (1), the literature did not seem to offer a cohesive answer regarding strong predictors of opioid abuse, and

even if it did, it was regarding a particular class of opioids that was too narrow a classification to be of any use to our model. Regarding (2), the additional consideration of a combination compartment added extra difficulties on top of the issue of data scarcity. Transitions between the combination compartment and other adjacent compartments were difficult to quantify numerically, and there was little if any research into the dynamics of such transitions. Accordingly, the combination compartment was eventually removed in the final model. Finally, as a direct consequence of data limitations, we had to limit the nonpharmaceutical opioid category to only include heroin. Although originally we aimed to analyze the part that fentanyl had to play in Maine's opioid epidemic, there was not enough available data to accomplish this goal. Furthermore, the specification to heroin seemed the best option as current data on nonpharmaceutical opioids give particular consideration to heroin, while fentanyl is a rather recent trend.

Problem Data

As anticipated, data availability posed a significant hurdle throughout this work. The complicated process in obtaining such data is discussed here. Data was used both for model fitting and determining parameters related to treatment and overdose.

To determine the number of individuals in A_P and A_H, data from the National Survey on Drug Use and Health (NSDUH) annual state prevalence estimates were used for the years 2014-18 [45, 46, 47, 48]. These data are shown in Table 2. Regarding A_P estimates, NSDUH provides prevalence estimates for (i) the nonmedical use of prescription pain-relievers (PPR) in the past year (IPY), and (ii) pain reliever use disorder (PRUD) in the past year. The latter was used as a proxy to estimate the number of Mainers in A_P. Further complicating compartment population estimates is that the latter metric was unavailable for years before 2016. To account for this setback, it was assumed that a certain proportion of the population nonmedically using prescription pain relievers will

manifest in a substance use disorder. Taking the mean of the proportions for the years in which pain reliever use disorder was measured, this corresponds to a percentage equal to roughly 20.36%. With this figure we can estimate the number of individuals with a prescription opioid use disorder in the years that the NSDUH data is unavailable (see bold entries in Table 2). Strangely, NSDUH did not report state prevalence estimates for the nonmedical use of prescription pain-relievers for the year 2014-2015. This percentage was simply taken to be the average of the previous and following year estimates (see italicized entry in Table 2). Finally, heroin use in the past year was used to estimate the number of Mainers in A_H.

Year	Adult pop.	Nonmedical use of PPRs IPY %	PRUD IPY %	Heroin use IPY %
2013-2014	1077372	3.08	**0.63**	0.52
2014-2015	1050169	*3.56*	**0.73**	0.62
2015-2016	1078498	4.03	0.75	0.52
2016-2017	1082085	4.04	0.80	0.55
2017-2018	1084107	3.75	0.85	0.7

Table 2: Yearly NSDUH data summary and Maine adult population.

To determine parameters related to treatment (i.e. η_P and η_H), data from the annual Substance Use Trends in Maine State Epidemiological Profile was used [2, 5, 7, 9, 15]. The only treatment data that was useful to our research was that pertaining to heroin/morphine, as no treatment data was provided explicitly for pharmaceutical

Year	Heroin/Morphine	Pharmaceutical opioids (estimate)
2014	3525	3064
2015	3423	2131
2016	3413	1816
2017	2975	1416
2018	3234	1306

Table 3: Yearly (primary, secondary, and tertiary) admission to treatment data for heroin/morphine and pharmaceutical opioids in Maine.

opioids. The total number provided in Table 3 is the sum of primary, secondary, and tertiary admissions for the respective drug category in that given year. When admitted to treatment, an individual identifies a primary, secondary, and sometimes tertiary drug as the reason for seeking treatment. Since pharmaceutical opioids were not explicitly characterized in epidemiological profiles, numbers were estimated from what data was available. Based on the results of [29], 76% of those admitted for buprenorphine/naloxone reported that they had obtained the opioid illicitly. However, state epidemiological profiles report buprenorphine in combination with methadone, making distinction between pharmaceutical and nonpharmaceutical sources more complicated. For simplicity, it was assumed that half of each non-heroin category were obtained via prescription. These estimates are also given in Table 3. These treatment data, in combination with the NSDUH data discussed above, are used to calibrate model parameters (see next subsection).

Both treatment parameters in the model were found by taking the average treatment rate for each year listed. An average value was favored over a linear fit to minimize forecasting bias. Parameters related to opioid overdoses, μ_P and μ_H, were obtained in a similar manner but based on annual drug death reports for the state of Maine, among other sources [42, 79, 80, 81, 82]. In this case, distinction was made between overdoses attributed to either heroin or pharmaceutical opioids. These data are presented in Table 4.

Year	Heroin deaths	Pharmaceutical opioid deaths	Source
2014	58	87	[42, 79]
2015	107	81	[79]
2016	119	72	[80]
2017	88	71	[81]
2018	74	52	[82]

Table 4: Drug death report data for heroin and pharmaceutical opioids.

Parameter Fitting

The only parameters in which reliable estimates were unable to be obtained were the duration individuals remain in treatment (τ), the rate at which individuals will transition to heroin use within a year of abusing pharmaceutical opioids (γ), and the transmission rate (β). To accommodate this, the system in (13) was fitted to the available data for the years 2014-2018 using the lsqcurvefit algorithm in MATLAB. This function uses the method of least-squares to determine opitmal parameter estimates. The parameters produced by the best-fit will minimize the sum of squared residuals between the model in (13) and the data used for model calibration discussed in the previous subsection. The best fit was produced for the values $\tau = 1.125$, $\gamma = 0.1219$, and $\beta = 13.286$, with error shown in Figures 7, 8, and 9. The initial guesses chosen for fitting were $\tau = 2$, $\gamma = 0.11$, and $\beta = 1$.

The value of τ indicates that the average length of treatment for individuals abusing opioids is approximately $1/1.125 = 0.89$ years, or around 10-11 months. This is understandable, as opioid addiction treatment tends to be longer in order to produce more favorable results. For example, methadone treatment of opioid addiction can last upward of 12 months [17]. The transition rate $\gamma = 0.1219$ implies that around 1 in 8 Mainers will develop heroin use disorder within a year of abusing pharmaceutical opioids. This value is close to similar results in the literature. For example, [22] states that 4-6% of people who "misuse" prescription opioids transition to heroin. In [49], between the groups studied, they found that on average about 11% of individuals abusing pharmaceutical opioids initiate heroin use within a year.

It is also worth mentioning here the results of parameter fitting other nonlinear mechanisms of transmission considered in our model. Various forms of nonlinear transmission can be found in similar models in the literature. An example of some possible nonlinear

terms, denoted by β_1, β_2, and β_3, incorporated in our model are given below:

$$\begin{aligned}
\dot{S} &= bN - \beta_1 S\frac{A_H}{N} - \varepsilon_P \rho S + \tau(1-\delta)R - \mu S \\
\dot{A}_P &= \varepsilon_P \rho S - \gamma A_P - \eta_P A_P - \beta_2 A_P \frac{A_H}{N} + \tau\delta R\left(\frac{A_P}{A_P + A_H}\right) - (\mu + \mu_P)A_P \\
\dot{A}_H &= \gamma A_P - \eta_H A_H + \beta_1 S\frac{A_H}{N} + \beta_2 A_P \frac{A_H}{N} + \beta_3 R\frac{A_H}{N} + \tau\delta R\left(\frac{A_H}{A_P + A_H}\right) - (\mu + \mu_H)A_H \\
\dot{R} &= \eta_P A_P + \eta_H A_H - \beta_3 R\frac{A_H}{N} - \tau R - \mu R.
\end{aligned}$$

A nonlinear term can be considered wherever contact between individuals of different compartments is believed to result in disease transmission. The works in [28] and [84] consider a nonlinear relapse term (similar to β_3 above), while the former also study a nonlinear recruitment term from the susceptible population directly into the addicted compartment (similar to β_1 above). Since these nonlinear contact terms are difficult to quantify, estimates were produced via parameter fitting. Parameter fitting revealed that the only significant nonlinear contact rate occurred in the movement of individuals from A_P to A_H, or β_2 in the above model. Best-fit estimates for β_1 and β_3 each returned zero for a variety of initial guesses, indicating that the contribution of either mechanism was negligible in the final model. We propose two potential reasons as to why this is the case: (a) interactions among individuals as a means of transmission is not very significant overall, owing itself to Maine's largely rural population; or (b) successful transmission is most likely to occur between individuals in A_P and A_H, while the likelihood of transmission between individuals in A_H and the other two compartments is too small to appear significant.

Reason (b) suggests that those already abusing pharmaceutical opioids are more likely than the remaining population to develop a heroin use disorder via contact with heroin abusers. It has already been shown that a majority of heroin abusers first began abusing pharmaceutical opioids prior to their usage of heroin [39, 40, 59], so this compartment could be more vulnerable to initiating heroin use than the susceptible population. If

this were the case, however, then individuals in recovery would also possess such a predisposition, but we have already seen that they do not based on the parameter fitting. Thus, we conclude that the neglibility of nonlinear forms of transmission in our model has more to do with Maine's low population density than with any predisposition to developing a heroin use disorder an individual may possess.

CHAPTER IV

ANALYSIS OF THE OPIOID EPIDEMIC MODEL

Mathematical characteristics of the model are elucidated, a local and global sensitivity analysis is performed on various quantities of interest, and projections are made for the next five and ten years with various control methods implemented, as well as with their respective 95% confidence intervals.

Well-posedness and Behavior of the Model

The mathematical model in (13) is well-posed in the following domain:

$$\Omega = \left\{(S, A_P, A_H, R) \in \mathbb{R}^4 \;\middle|\; S > 0,\ A_P > 0,\ A_H > 0,\ R > 0\right\}.$$

To see this, note that the partial derivatives of (13) exist and are continuous on Ω, which is sufficient in showing that if $x_0 \in \Omega$, then the initial value problem $\dot{x} = f(x)$, $x(0) = x_0$ has a unique solution by Theorem 2.1.1.

The trajectories of the system in (13) are given in Figure 3. Let $N = S + A_P + A_H + R$ denote the total population considered in our model. We do not assume the population to be constant, as our projections are for 5-10 years into the future. Summing the system of differential equations yields the relation

$$\frac{dN}{dt} = bN - \mu N - \mu_P A_P - \mu_H A_H. \tag{14}$$

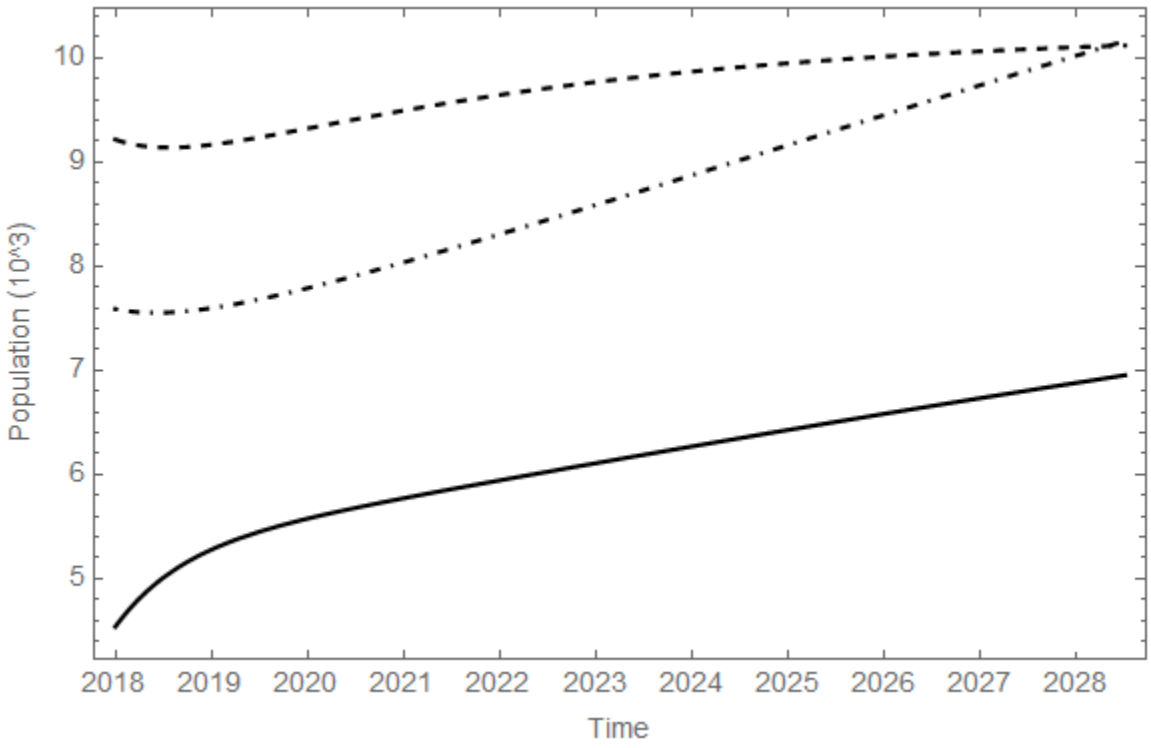


Figure 3: Trajectories of the compartments A_P (dashed), A_H (dot-dashed), and R (solid) over a ten year time interval. Trajectories were obtained by numerically solving the system in (13).

Letting $r = b - \mu$, we arrive at the equation

$$\frac{dN}{dt} = rN - \mu_P A_P - \mu_H A_H.$$

In terms of population modeling, this is an exponential growth model with growth rate r and "harvesting" attributed to overdose deaths of individuals with POUD and HUD. An exponential growth model was deemed appropriate as such assumptions produce sufficient approximations for large populations over small time scales [34].

It remains to discuss any equilibria of the system. Unfortunately, the system does not possess any! Although this does not appear obvious, it becomes intuitive when one realizes that individuals develop addiction to pharmaceutical opioids at a linear rate via the addiction term ε_P. Thus, a disease-free equilibrium cannot exist as “infected” individuals are constantly being produced, even when those categories are absent (i.e.

when $A_P = A_H = 0$). An endemic equilibrium does not exist either, as no numerical solution to $f(x) = 0$ exists. With these model properties in mind, a conventional analysis involving reproduction number quantification was not possible. Instead, more general analysis techniques were applied.

Unless otherwise mentioned, all simulations of the model in (13) were performed using a continuous-time Markov chain, where inter-event times were assumed to obey an exponential distribution.

Parameter Uncertainty

To quantify the uncertainty in our parameter fits, we use the parameter uncertainty techniques discussed in [38]. The fundamental idea of the following parameter uncertainty method is assuming an error structure of the best-fit parameter values (in this case, a Poisson error structure [26, 76]), generating new best-fit parameters from this error structure, and then re-fitting the model using the new parameter values to obtain a completely new model forecast. We let q denote the number of data points and assume we are fitting i parameters. For clarity, the algorithm is given below in step-by-step fashion.

1. Letting t_j denote the data points, for $j = 1, 2, \ldots, q$, we first fit the model to the data to obtain the best-fit parameter estimates, denoted by $\hat{\boldsymbol{\theta}} = (\theta_1, \theta_2, \ldots, \theta_i)$. The best-fit function shall be denoted as $\hat{f}(t_j, \hat{\boldsymbol{\theta}})$.

2. Next, the cumulative sum function of the data is constructed as follows:

$$F(t_j, \hat{\boldsymbol{\theta}}) = \sum_{k=1}^{j} \hat{f}(t_k, \hat{\boldsymbol{\theta}})$$

   for $j = 2, 3, \ldots, q$.

3. New data is generated and S new fits are produced in the same manner, denoted $f_1(t_j,\hat{\boldsymbol{\theta}})$, $f_2(t_j,\hat{\boldsymbol{\theta}})$, ..., $f_S(t_j,\hat{\boldsymbol{\theta}})$. The number of new fits generated is arbitrarily chosen, and is typically a large number to sufficiently illustrate the extent of model forecast uncertainty.

4. The new data are generated by assuming that the difference in data points of the cumulative sum function obeys a Poisson error distribution, so that we have

$$f_m(t_j,\hat{\boldsymbol{\theta}}) = \text{Po}(F(t_j,\hat{\boldsymbol{\theta}}) - F(t_{j-1},\hat{\boldsymbol{\theta}}))$$

for $j = 2,3,\ldots,q$, and $m = 1,2,\ldots,S$. We additionally require that

$$f_1(t_1,\hat{\boldsymbol{\theta}}) = f_2(t_1,\hat{\boldsymbol{\theta}}) = \cdots = f_S(t_1,\hat{\boldsymbol{\theta}}).$$

For our particular case, we fit the numerical solutions of $\dot{A_P}$,$\dot{A_H}$, and $\dot{R}$ in (13) to the NSDUH data. We omitted additionally fitting the trajectory defined by $\dot{S}$ as the suscep-

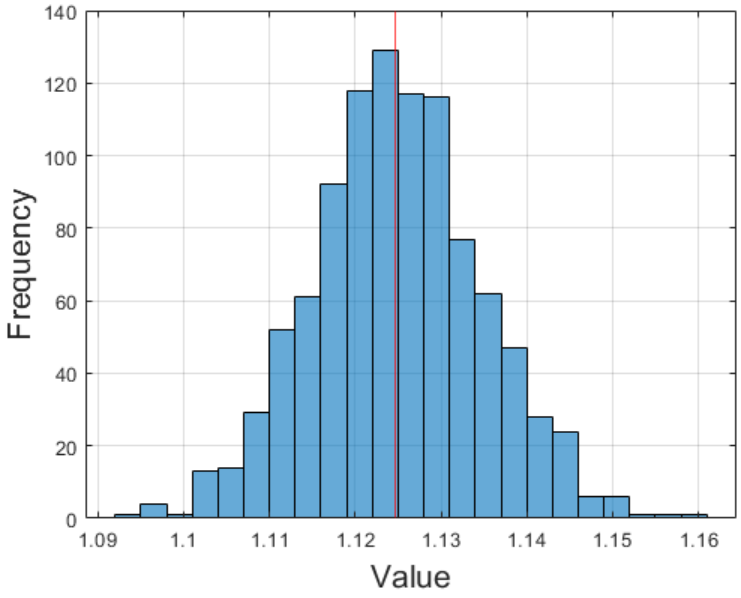
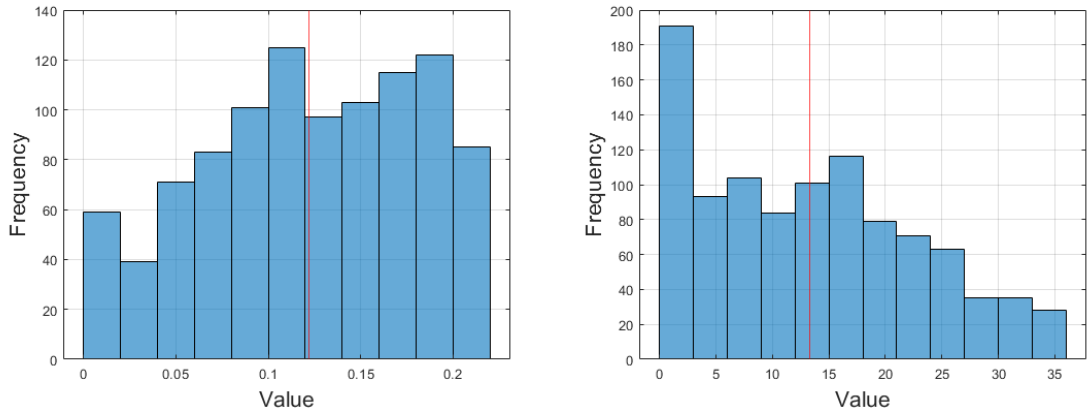


Figure 4: Distribution of τ following 1000 bootstrap iterations. The red vertical line is the best-fit value of τ obtained from parameter fitting.



(a) (b)

Figure 5: Distribution of (a) γ and (b) β following 1000 bootstrap iterations. The red vertical line in either histogram is the mean of the plotted data.

tible compartment was orders of magnitude larger than the remaining compartments, and not much accuracy overall was sacrificed in order to obtain a greater degree of certainty in fitting the model to the compartments we are most concerned with analyzing. For our model there are $i = 5$ data points and three parameters we wish to quantify the uncertainty of (τ, γ, and β). We perform the algorithm for $S = 1000$ generated model forecasts. The distribution of τ is provided in Figure 4, while the distributions of γ and β are given in Figures 5a and 5b, respectively.

Indeed, the distributions of β and γ are much different than that of τ. For many of the algorithm runs, best-fit estimates converged to zero or a near-zero value for either β or γ. To help illustrate this back-and-forth convergence, a plot of the (γ, β) plane is given in Figure 6 after the 1000 bootstrapped simulations, with the red dot denoting the best-fit values used in the model. An inverse relationship between the parameters is clear, as both parameters dictate methods of movement from A_P to A_H. Since convergence most of the time did not favor nonzero values for both γ and β, it can be inferred that only one mechanism of movement contributes more so to the transition of individuals from abusing pharmaceutical opioids to the initiation of heroin use. Because the linear term γ is intentionally generic in its definition, we rather scrutinize the significance of

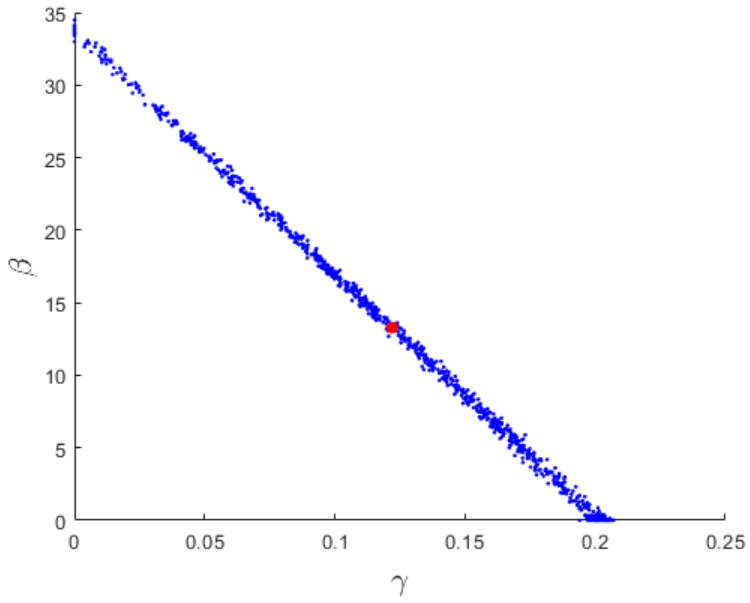


Figure 6: Plot of the best-fit values of β and γ for the 1000 generated model forecasts.

β, as this parameter has a more concrete interpretation. In particular, β is the force of transmission between individuals in A_H and A_P. From the graph in Figure 6, as well as in 5b, we see that the best-fit value of β converged to zero more frequently than γ. We conclude from this that γ contributes most significantly to the movement of individuals from A_P to A_H. As an aside, this finding supports the claim made in the previous subsection about Maine's rural population accounting for the reduced significance of nonlinear forms of transmission in the model.

Using the bootstrapped parameter values, we can see the corresponding uncertainty in our model predictions in forward time (see Figures 7, 8, and 9). In Figure 7 is a graph of the NSDUH data used to calibrate the A_H compartment as well as A_H curves for each bootstrapped parameter estimate from the previous algorithm. In a similar fashion, Figures 8 and 9 present the same information but for A_P and R, respectively. In some instances the projected curves deviate from the original data points more than we would like them to, but this can be explained by the scarcity of data and the fact that we are fitting the model to three curves simultaneously. This uncertainty can be

mitigated as more data becomes available, but even with the small number of years in which data is available, the spread is qualitatively narrow even after ten years.

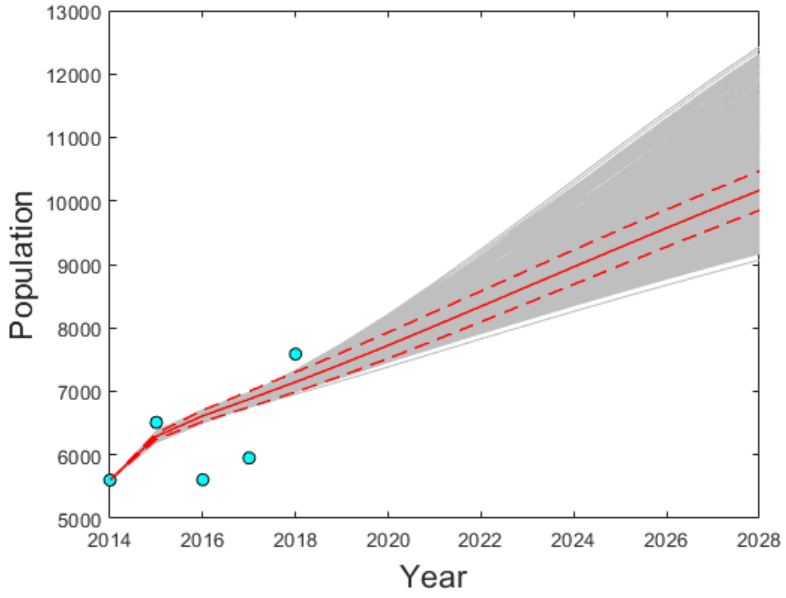


Figure 7: Bootstrapped curves of A_H from parameter uncertainty quantification. Gray curves are the bootstrapped curves, the red curve is the original best fit line, and the red dashed lines are curves at either extreme of each parameter's 95% confidence interval. The cyan circles are the NSDUH data values used for fitting the model.

Local Sensitivity Analysis

Of interest is how state variables change with respect to changes in parameters. Small perturbations to parameters and quantifying changes in model results can help us to determine influential parameters and inform control strategies accordingly. The system in (13) can be written as $\dot{x} = f(x,\theta)$, where $x = (S,A_P,A_H,R)$ is the state variable vector and θ is the parameter vector which has 10 components From Table 1 (we omit natural birth and death rates, b and μ, respectively, from the analysis by viewing them as constants). To find the sensitivity of each state variable in x to each parameter, we derive the sensitivity system in Theorem 2.3 for (13). We omit the full 4×10 set of equations here, but as an example the sensitivity of the state variables to changes in ρ

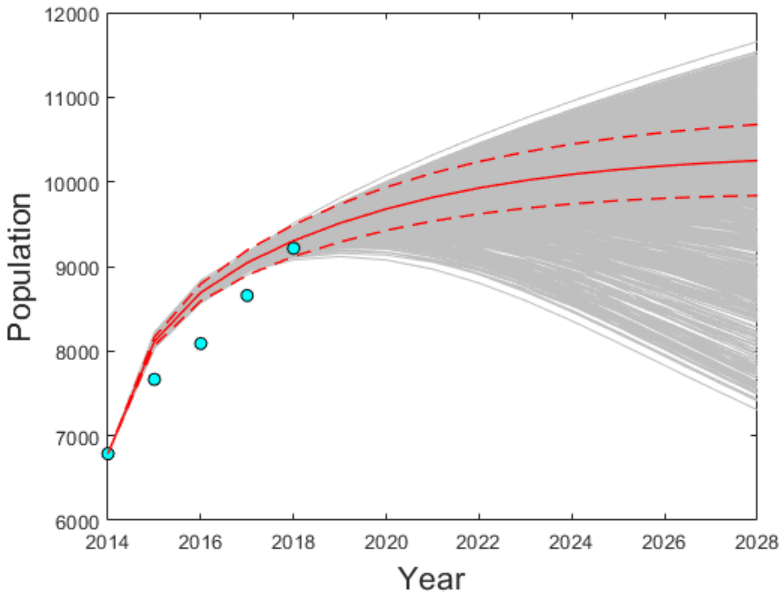


Figure 8: Bootstrapped curves of A_P from parameter uncertainty quantification. Gray curves are the bootstrapped curves, the red curve is the original best fit line, and the red dashed lines are curves at either extreme of each parameter's 95% confidence interval. The cyan circles are the NSDUH data values used for fitting the model.

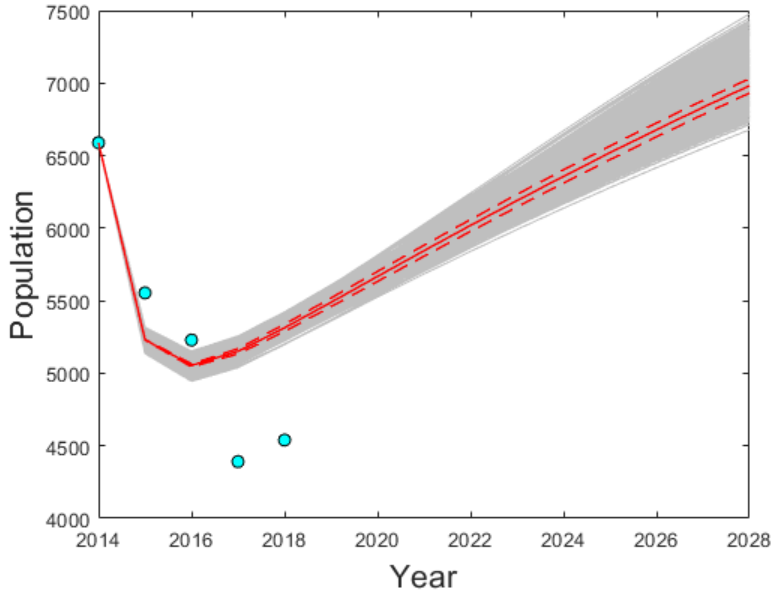


Figure 9: Bootstrapped curves of R from parameter uncertainty quantification. Gray curves are the bootstrapped curves, the red curve is the original best fit line, and the red dashed lines are curves at either extreme of each parameter's 95% confidence interval. The cyan circles are the NSDUH data values used for fitting the model.

is given below. From the system in (6), we let

$$\Phi = \begin{pmatrix} \frac{\partial S}{\partial \rho} & \frac{\partial A_P}{\partial \rho} & \frac{\partial A_H}{\partial \rho} & \frac{\partial R}{\partial \rho} \end{pmatrix}'$$

and obtain

$$\begin{aligned} \frac{\partial}{\partial t}\Phi &= \frac{\partial f}{\partial x}(x(t,\theta_0),\theta_0)\Phi + \frac{\partial f}{\partial \theta}(x(t,\theta_0),\theta_0) \\ &= \frac{\partial f}{\partial x}(x(t,\rho_0),\rho_0)\Phi + \begin{pmatrix} -S\varepsilon_P \\ S\varepsilon_P \\ 0 \\ 0 \end{pmatrix} \end{aligned}$$

where

$$\frac{\partial f}{\partial x} = \begin{pmatrix} b-\mu-\rho\varepsilon_P & b & b & b+(1-\delta)\tau \\ \beta A_P \frac{A_H}{N^2}+\rho\varepsilon_P & \beta A_P \frac{A_H}{N^2}-\beta\frac{A_H}{N}-\gamma-\mu-\eta_P-\mu_P \\ -\delta\tau R\frac{A_P}{(A_H+A_P)^2}+\delta\tau\frac{R}{A_H+A_P} & \beta A_P \frac{A_H}{N^2}-\beta\frac{A_P}{N}-\delta\tau R\frac{A_P}{(A_H+A_P)^2} & \beta A_P \frac{A_H}{N^2}+\delta\tau\frac{A_P}{A_H+A_P} \\ -\beta A_P \frac{A_H}{N^2} & -\beta A_P \frac{A_H}{N^2}+\beta A_H \frac{1}{N}+\gamma \\ -\delta\tau R\frac{A_H}{(A_H+A_P)^2} & -\beta A_P \frac{A_H}{N^2}+\beta\frac{A_P}{N}-\mu-\mu_H-\eta_H & -\beta A_P \frac{A_H}{N^2}+\delta\tau\frac{A_H}{A_H+A_P} \\ 0 & \eta_P & \eta_H & -\mu-\tau \end{pmatrix}$$

and all variables and parameters above are evaluated at their reference values (ρ_0 denotes the reference value of the parameter ρ).

After the sensitivity functions are calculated, they are normalized. These normalized functions at any time t give the relative sensitivity of a state variable of the model to a particular parameter. Let Φ denote the sensitivity system matrix derived in (6). Let Φ_i^j denote the (i,j) entry of Φ (e.g. $\Phi_{A_P}^{\rho}$ represents the sensitivity of A_P with respect to ρ). The relative sensitivity of the i^{th} state variable with respect to the j^{th} parameter is

given by

$$\frac{\frac{\partial x_i}{\partial \theta_j}(t,\theta_0)}{\frac{x_i(t,\theta_0)}{\theta_j}} = \frac{\partial x_i}{\partial \theta_j}(t,\theta_0)\cdot\frac{\theta_j}{x_i(t,\theta_0)} = \Phi_i^j(t)\cdot\frac{\theta_j}{x_i(t,\theta_0)}.$$

The reference trajectories of the system are given in Figure 3, while the sensitivity of the state variables A_P, A_H, and R to each parameter as time varies is given in Figure 10.

From the sensitivity plots in Figure 10, we see that A_P is very sensitive to changes in the treatment rate of heroin abusers (η_H). This is likely explained by our relapse re-entry assumption discussed previously. In particular, as the number of individuals in A_P grows larger, relapsed individuals will more likely re-enter A_P than A_H. Thus, as treatment for η_H increases, A_H will shrink in size, and more individuals upon relapsing will enter A_P. A_P is also sensitive to local changes in the parameter δ. The relative sensitivity of A_P to δ increases for a short time, until a plateau is obtained at around the 4 year mark. This is in contrast with the bowed appearance of the relative sensitivity of A_P to other influential parameters, such as ε_P and ρ. This indicates that changes to δ manifest quickly in effects that do not vary significantly over time, while changes to ε_P and ρ take longer to reach their full potential in the system. A strong inverse relationship is observed in the sensitivity of A_P to the treatment rate of pharmaceutical opioid abusers, η_P. The flatter appearance of the curve also indicates that changes to η_P are quicker to manifest in changes to A_P than changes to either ε_P or ρ. An interesting situation is observed in the case of the treatment rate of heroin abusers, η_H. This phenomenon can once again be explained by the dynamics assumed in the system. That is, as more individuals in A_H seek treatment, A_H will decrease and size more individuals relapsing are assumed to re-enter A_P, as this rate is proportional to the fraction $A_P/(A_H+A_P)$.

In contrast to the situation with A_P, the parameters η_P and ρ are not nearly as influential to A_H, as neither parameter dictates a direct route of transmission into or out of A_H. Of interest is the sensitivity of A_H to the parameter δ. This is certainly the most influential parameter, indicating that relapse most strongly determines the size of A_H. Even if

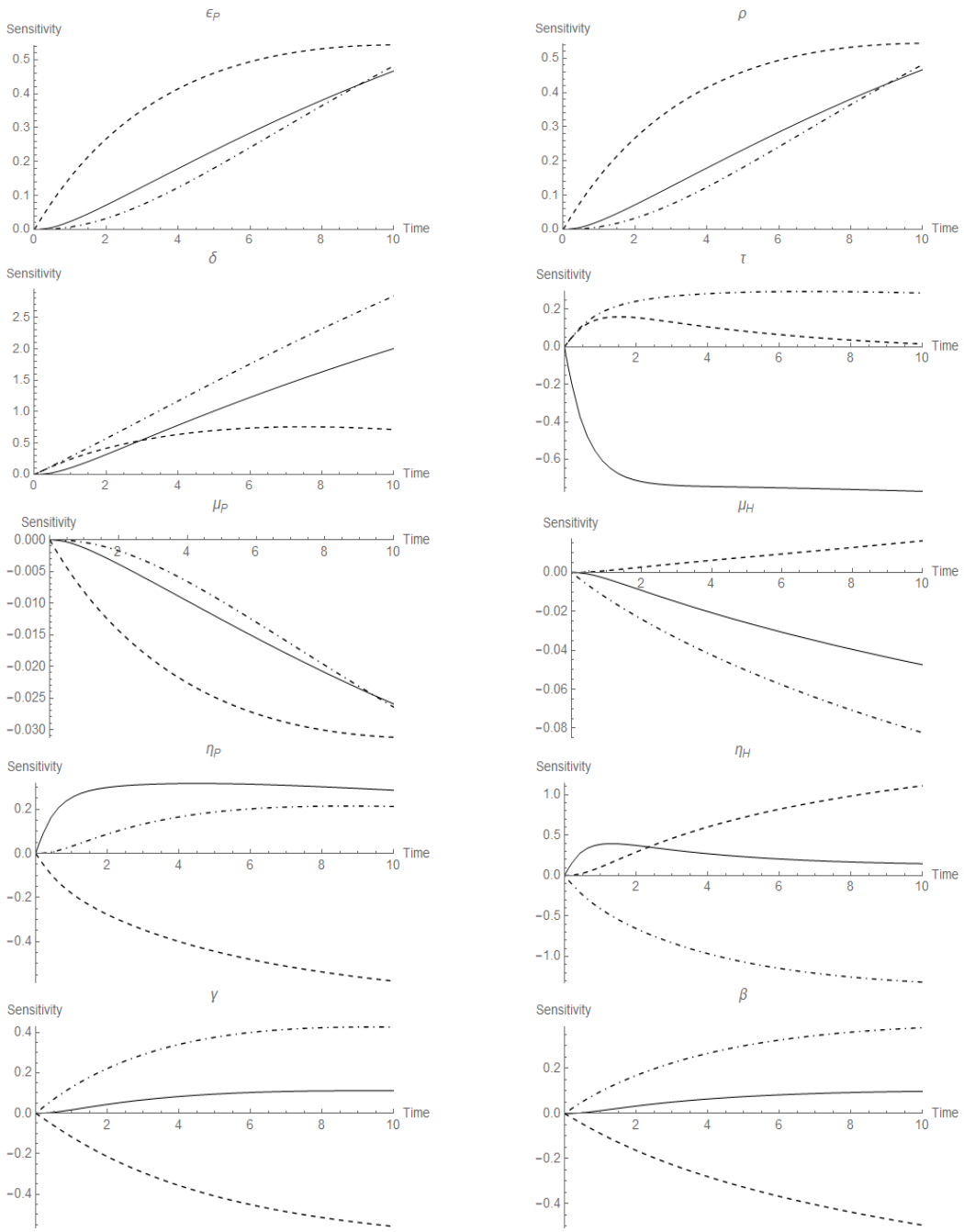


Figure 10: Local sensitivity of the variables A_P (dashed), A_H (dot-dashed), and R (solid) to select model parameters with respect to time. The parameter depicted in each graph is given at the top of each individual plot.

following relapse, individuals enter A_P, they are still capable of progressing to A_H. We may conclude that, in this way, A_H is more directly impacted by relapse than A_P. The sensitivity graph of γ reveals that small perturbations effect little change on A_H over

time, as is the case with β. As mentioned previously, η_H is an influential parameter, as expected, as this parameter is responsible for the removal of individuals from A_H. The reason η_H is not as influential as potentially anticipated is because the rather high value of δ assures that, so long as $A_H/(A_P+A_H)$ is not too small, a significant portion of individuals recovering from A_H will relapse.

Finally, the sensitivity of R to various parameters is discussed. The sensitivity of R to ρ and ε_P are similar to that of A_H, as neither parameter directly contributes to individuals entering or exiting R, and thus the relative sensitivity is approximately linear. R is more sensitive to δ, as a larger value of δ will produce a larger number of infected individuals overall, and thus the number of individuals entering treatment increases. The treatment completion rate τ produces the most negative effect on R, as an increase in the value of τ shortens the overall time that individuals spend in R. Increases in the treatment rates η_P and η_H increase the number of individuals seeking treatment, hence the behavior in their respective sensitivity plots.

Global Sensitivity Analysis

Local sensitivity analysis measures the effects of *small* perturbations in model parameters, but what if we are interested in testing combinations of parameter values over a larger region of possible values? To assist in quantifying the effects of large changes to parameter values, global sensitivity analysis is performed. Note that a global analysis of sensitivity depends strongly on sufficient sampling of the parameter space, which is a drawback not shared by the previous sensitivity analysis method. When possible, such as for the parameters that were fitted to model data using the least-squares method, the parameter range listed in Table 1 is the 95% confidence interval. This also includes parameters that were calculated from existing data, such as the treatment rates, η_P and η_H, and the overdose rates, μ_P and μ_H. For the remaining parameters, their respective

ranges were estimated.

For this analysis, we use the elementary effects method, as outlined in Chapter II, for $r = 30$ trajectories, $p = 4$, and $\Delta = 1$. As stated, the respective range $[x_i^L, x_i^U]$ for each parameter we are analyzing is given in Table 1. An efficient means of computing the elementary effects of every parameter all at once is presented here [36, 65]:

1. For each trajectory, choose a base vector $(x_1, x_2, \ldots, x_n) \in \{1, 2, \ldots, p-1\}^n$ for some p.

2. Choose $1 \leq i \leq n$ so that we also have the vector $(x_1, \ldots, x_i + \Delta, \ldots, x_n)$.

3. Compute the elementary effect of x_i, or

$$ee(x_i) = \frac{f(y_1, y_2, \ldots, y_{i,\Delta}, \ldots, y_n) - f(y_1, y_2, \ldots, y_i, \ldots, y_n)}{\Delta},$$

   and choose $j \neq i$ for $1 \leq j \leq n$.

4. Repeat the process for x_j until all factors have been accounted for.

Recall that

$$y_i = x_i^L + x_i(x_i^U - x_i^L)(p-1)$$

and $y_{i,\Delta}$ is simply the scaled value of $x_i + \Delta$. The model outputs that we measure the sensitivity of are average populations of A_H, A_P, and $A_H + A_P$ over five and ten year intervals. The results of the analysis after five years are shown in Figure 11, and the corresponding results for the ten year simulation is given in Figure 12.

The average and standard deviation of the elementary effects of a parameter, denoted μ and σ, respectively, are calculated. Recall that μ quantifies sensitivity of the model output to changes in the parameter, and the value of σ is used to determine if changes to model output with respect to changes in a parameter is linear, or otherwise (due

to nonlinearity and/or coupled interactions of the factor of interest). Additionally, the average of the absolute values of the elementary effects of each parameter, denoted by μ^*, is calculated as well, as done in [35]. As per the suggestion of [75], the (σ,μ) and (σ,μ^*) planes are plotted for each model output studied (see Figures 11 and 12).

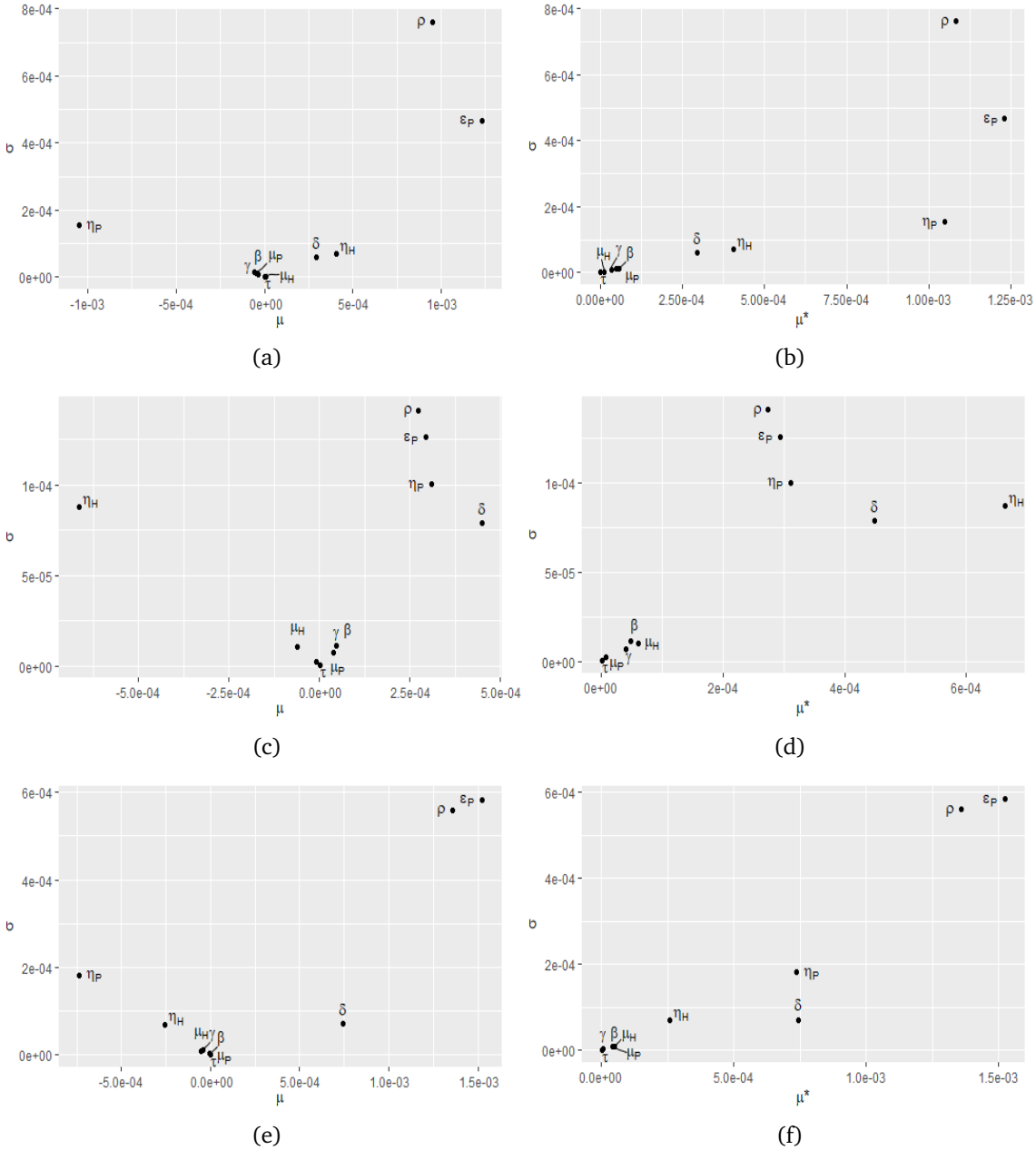


Figure 11: Morris method results for each metric tested after five years. (a)-(b) are the (σ,μ) and (σ,μ^*) planes of the results for the average number of individuals in A_P, while those for A_H and $A_P + A_H$ are given in (c)-(d) and (e)-(f), respectively

Note that for all parameters analyzed, σ, μ, and μ^* are rather small. This is because the changes produced in model outputs (i.e. the average values of A_P, A_H, and $A_P + A_H$) were each divided by the total population in the system, which is on the order of 10^6. Therefore, these quantities should be understood as relative rather than insignificant. For the average number of individuals in A_P after five years, the most influential parameters appear to be the addiction rate of pharmaceutical opioids (ε_P), the proportion of Mainers with an opioid prescription (ρ), and the treatment rate of individuals with a pharmaceutical opioid use disorder (η_P), in that order. Interestingly, η_P and especially ρ exhibit strong nonlinearity, as evident by their large values of σ. This is most likely a result of both parameters belonging to the same expression. This same phenomenon occurs when analyzing the average number of individuals in A_H after five years, albeit to a lesser extent. In the case of this model output, the treatment rate of heroin abusers (η_H) is the most influential. This partly agrees with the local sensitivity analysis carried out in the previous subsection after five years, as the local analysis identified η_H as very influential, but the treatment relapse probability (δ) and η_H had much more comparable influence at $t = 5$ years, unlike the global sensitivity analysis results.

For the sum of both addicted compartments, ε_P and ρ appeared the most influential. The average number of individuals in A_P during a simulation tends to be larger than the average number of individuals in A_H (see Figure 3), as addiction to prescription opioids is more easily facilitated and thus more common than addiction to illicit opioids. Given this and the underlying assumptions about our system (specifically concerning the movement of individuals from A_P to A_H), parameters influential to the average value of A_P will also be influential to the total sum of drug abusers in the system. The relapse probability δ is also identified as significant. This is because a larger relapse probability will cause a greater number of individuals seeking treatment to re-enter either addicted compartment. The treatment rate η_P also stands out as significant, but likely for the same reasons as ε_P and ρ, given the smaller values of μ and μ^* obtained by these

parameters in Figures 11 (e)-(f) as compared to in Figures 11 (a)-(b). For all aforementioned model outputs, the rate of progression from pharmaceutical opioid abuse to heroin abuse (γ), the contact rate between individuals in either addicted compartment (β), the treatment completion rate (τ), and the death rates consistently ranked poorly in terms of global sensitivity. This somewhat agrees with the local analysis, but the disparity is much more evident.

The results of the global sensitivity analysis for the aforementioned metrics at 10 years are given in Figure 12. For the average value of A_P after 10 years, ε_P, ρ, and η_P appear again as influential parameters. However, ε_P now exhibits more nonlinear behavior than ρ. η_H and δ appear as lesser significant parameters. For the average value of A_H, the parameters ρ, ε_P, δ, and η_H appear as most significant, while η_P much less so, in contrast with the sensitivity analysis performed at five years. Also in contrast with the previous analysis is that the parameter effects are not as disparate as they were prior. Rather, the most influential parameters are closer in terms of their respective μ^* values, illustrative of similar long-term effects. Finally, for the average combined sum of either compartment, similar results are obtained as in the five year analysis, with δ slightly more influential than η_P. This shows that in the longer term, reducing relapse probability has a greater overall effect on controlling the number of opioid abusers in the system than treatment, agreeing with the local sensitivity analysis.

Control Methods

One of the objectives of this study is to investigate the effectiveness of different means of controlling the opioid epidemic in Maine. To do this, control measures already implemented or theorized can be tested against the mathematical model to ascertain their respective level of effectiveness. To test a control method with the mathematical model, one need only adjust the relevant parameters in accordance with whatever changes are

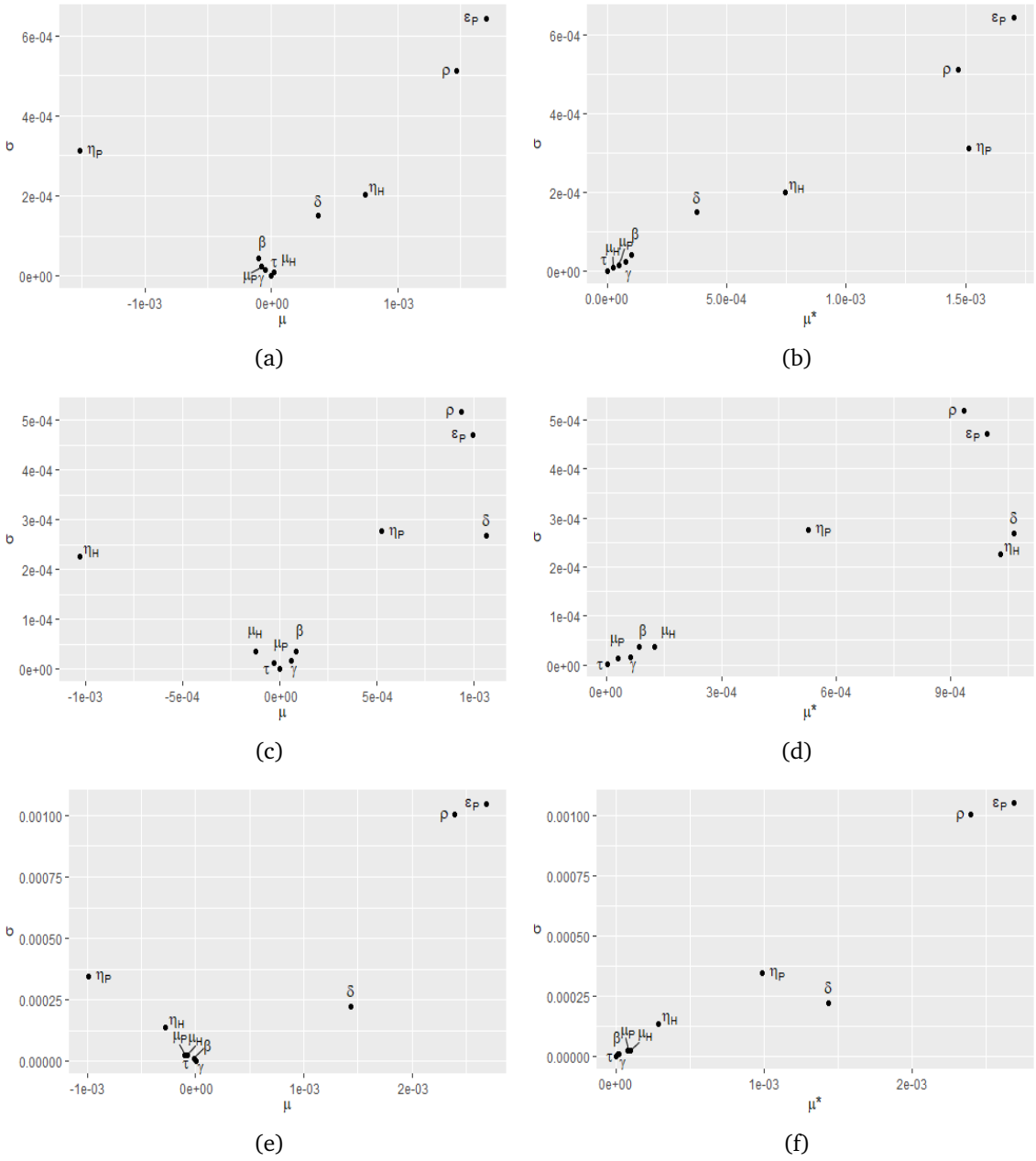


Figure 12: Morris method results for each metric tested after ten years. (a)-(b) are the (σ,μ) and (σ,μ^*) planes of the results for the average number of individuals in A_P, while those for A_H and A_P+A_H are given in (c)-(d) and (e)-(f), respectively

brought about with the respective control strategy, as done in [73]. For control strategies that limited prescriptions of opioids, heroin accessibility/usage was not assumed to increase, in accordance with recent findings [40, 61], with the exception of drug reformulation. An explanation of each control strategy is provided below:

1. **Prescription monitoring program (PMP)**: Maine's Prescription Monitoring Program was first implemented in 2004 in response to the growing problem posed by prescription drugs [58]. The PMP was intended to decrease opioid prescriptions overall to help "prevent adverse drug-related events" [8]. Since this program has been around for over a decade, including this control strategy is to account for the *growth* of the program in the future. Examples of such growth can be found in the passing of L.D. No. 1646 in 2016 [4], which addressed issues of information sharing and set additional requirements for dispensers and prescribers, among other things, and the recent approval of L.D. No. 2117 [16], which requires "dispensers to report all prescription drugs dispensed intended for human consumption rather than controlled substances only." As more prescribers and dispensers use the PMP more frequently, more patient information becomes available, and as Maine adjusts to legislation expanding the PMP in recent years, we can account for this with a decrease in the number of Mainers with an opioid prescription. We assume that this proportion (ρ) is decreased by 2.5%.

2. **Medication-assisted therapy (MAT)**: Maine Governor Janet Mills signed an executive order in 2019 to address the opioid epidemic in the state of Maine. Within the executive order was exploring the integration of MAT into the criminal justice system and reviewing MAT-related insurance limitations [14, 24]. Since expansions to MAT largely concern inmates, and thus less than 0.3% of the population [12], the overall effect was assumed modest, which we represent by a 2.5% decrease in treatment relapse probability (δ).

3. **Increase treatment accessibility**: Opioid treatment is difficult to obtain for the uninsured and those relying on Medicaid in Maine [60]. Increasing treatment accessibility in the form of expanding Medicaid or therapist reimbursement will help to make treatment more available to Mainers. It was assumed that such a

change would increase annual treatment rates (η_P and η_H) by 5%.

4. **Expand Naloxone availability**: Naloxone is an opioid antagonist that reverses the effects of an opioid overdose. Indeed, Gov. Mills in her executive order in 2019 sought to make Naloxone "more widely and readily available, accessible and affordable" [14]. The main intention of this is to reduce the number of overdoses and deaths attributed to opioids. As Naloxone becomes more available, we assume a 5% reduction in mortality for both pharmaceutical opioids and heroin (μ_P and μ_H, respectively).

5. **Drug reformulation**: In response to the addictive nature of opioids, some painkillers have been reformulated to deter their misuse. To model this, we decrease ε_P by 10%. The work in [74] and [30] suggest that drug reformulation was a direct factor in the increase of injection rates among heroin users. To account for this in our model, the rates responsible for the transition of pharmaceutical opioid abusers to heroin (γ and β) were each increased by 5%. Chilcoat et al. [37] also found that reformulated opioids reduced doctor-shopping rates, and thus the proportion of Mainers with opioid prescriptions (ρ) was reduced by 2.5% to account for the decreased demand.

The control methods and the respective model changes used to test them are given in Table 5. Indeed, there exist control methods that have been implemented that are not listed above. Some examples include making recovery coaches available in emergency rooms, lifting limits to methadone treatment, and making suboxone more widely available in hospitals. However, the inclusion of these strategies in our analysis would be redundant, as the effect of each one can be inferred from the analysis of a method already listed in Table 5. For example, increasing accessibility to methadone treatment can be modeled by decreasing the relapse probability (δ), which we already explore in expanding access to MAT.

Control method	Baseline model changes
Prescription monitoring program (PMP)	Decrease ρ by 2.5%
Medication-assisted therapy (see [69])	Decrease δ by 2.5%
Increase treatment accessibility	Increase η_P and η_H by 5%
Expand Naloxone availability	Decrease μ_P and μ_H by 5%
Drug reformulation	Decrease ε_P by 10%, ρ by 2.5%, and increase γ and β by 5%

Table 5: A list of the control methods tested and the respective changes to model parameters used to simulate them.

Of course, control strategies are not implemented in a vacuum, so control strategies are also tested in combination to find the most effective approach overall. The metrics used to determine the effectiveness of each control method were the average number of individuals abusing pharmaceutical opioids (denoted $\overline{A}_P$), the average number of individuals abusing heroin ($\overline{A}_H$), the number of deaths due to pharmaceutical opioid overdose (D_P), and the number of deaths due to heroin overdose (D_H). Averages were taken over the entire simulation time. We ran 300 simulations for the baseline model and then for each control strategy to determine the extent that each intervention method in Table 5 affected these metrics on average. The results of these simulations after 5 years are given in Table 6, while the 10 year results are presented in Table 7.

From the results in Table 6, we see that expanding the PMP and MAT were the only strategies that yielded decreases in all the factors considered. MAT performed much

Control strategy	$\overline{A}_P$	$\overline{A}_H$	D_P	D_H
PMP	-0.676%	-0.0836%	-1.52%	-0.243%
MAT	-1.08%	-1.84%	-1.26%	-1.95%
Increase treatment accessibility	+0.39%	-2.85%	+0.475%	-2.80%
Expand Naloxone availability	+0.0480%	+0.230%	-5.04%	-5.10%
Drug reformulation	-5.56%	+1.20%	-5.71%	+0.984%

Table 6: Results of stochastic simulations testing various control strategies after 5 years. The percentages listed are percent changes from the baseline model value for that metric.

better in all areas except in reducing the number of overdoses due to heroin abuse, indicating that increasing the effectiveness of treatments (reducing δ) is more widely effective than reducing the number of prescriptions (reducing ρ). The remaining control strategies had mixed results. Increasing treatment accessibility reduced both the number of individuals abusing heroin, and the number of overdoses due to heroin, but slightly increased the number of individuals abusing pharmaceutical opioids and the number of overdoses due to pharmaceutical opioids. This is perhaps because $\eta_H > \eta_P$, and so those addicted to heroin are more likely to seek treatment. This makes A_H decrease over time, but the greater proportion of pharmaceutical opioid abusers in the system translates to more individuals relapsing into A_P. This trend is even more apparent after ten years (see Table 7). Expanding Naloxone availability was the most successful in reducing overdose deaths in either addicted compartment, but at the cost of a slight increase in the number of abusers in both A_P and A_H. This is most likely explained by individuals that would have died in the baseline simulation living to relapse, given the high value of δ. At ten years this is still the case, although the increase is more prevalent in A_H, as the increase in A_P even at 10 years is less than a tenth of a percent. Finally, drug reformulation proved even more successful in reducing overdoses attributed to pharmaceutical opioids, as well as significantly reducing the number of individuals abusing pharmaceutical opioids. However, heroin use rates increased as did heroin overdose deaths. Once again, this is because A_P shrinks, and so a greater proportion of relapsing addicts enter A_H. Interestingly, these increases are smaller after

Control strategy	$\overline{A}_P$	$\overline{A}_H$	D_P	D_H
PMP	-0.91%	-0.66%	-1.13%	-0.46%
MAT	-1.57%	-3.76%	-1.55%	-3.65%
Increase treatment accessibility	+1.29%	-4.03%	+1.39%	-3.99%
Expand Naloxone availability	+0.09%	+0.30%	-5.04%	-4.72%
Drug reformulation	-8.26%	+0.2%	-7.9%	+0.28%

Table 7: Results of stochastic simulations testing various control strategies after 10 years. The percentages listed are percent changes from the baseline model value for that metric.

Control strategies tested	$\overline{A}_P$	$\overline{A}_H$	D_P	D_H
PMP and MAT	-1.88%	-2.09%	-1.02%	-1.69%
Expanded Naloxone availability and drug reformulation	-5.45%	-1.16%	-9.24%	-4.06%
Expanded Naloxone availability and MAT	-1.02%	-1.81%	-5.67%	-6.69%
PMP and drug reformulation	-6.11%	+0.842%	-5.32%	+0.629%
Expanded Naloxone availability, increased treatment accessibility, and drug reformulation	-5.13%	-1.57%	-9.54%	-6.74%

Table 8: Results of stochastic simulations testing combined control strategies after 5 years. The percentages listed are percent changes from the baseline model value for that metric.

ten years.

Control strategy batch	$\overline{A}_P$	$\overline{A}_H$	D_P	D_H
PMP and MAT	-2.56%	-4.35%	-2.42%	-3.90%
Expanded Naloxone availability and drug reformulation	-8.18%	+0.45%	-12.38%	-4.18%
Expanded Naloxone availability and MAT	-1.48%	-3.65%	-5.99%	-8.26%
PMP and drug reformulation	-9.17%	-0.46%	-9.00%	-0.02%
Expanded Naloxone availability, increased treatment accessibility, and drug reformulation	-7.10%	-3.46%	-11.68%	-7.85%

Table 9: Results of stochastic simulations testing combined control strategies after 10 years. The percentages listed are percent changes from the baseline model value for that metric.

Control strategies were then tested together to elucidate interactions otherwise unobserved during simulations of individual tests. Control strategy combinations were determined based on mutual beneficence (i.e. an intervention strategy compensating for the shortcomings of another and vice versa) and greatest combined effect. Each batch consisted of only two control strategies, with the exception being the final batch, which combined three of the strategies. The tested batches are as follows: (a) PMP and

MAT, (b) expanded Naloxone availability and drug reformulation, (c) expanded Naloxone availability and MAT, (d) PMP and drug reformulation, and (e) expanded Naloxone availability, increased treatment accessibility, and drug reformulation. Five year results are given in Table 8, while ten year results are given in Table 9.

In the previous analysis, both the PMP and the MAT decreased the numbers and overdose deaths of either addicted compartment. When combined, more favorable results were obtained except in reducing the number of pharmaceutical opioid overdose deaths, in which either control strategy was more effective in reducing individually, and reducing the number of heroin overdose deaths, in which MAT was more effective at reducing individually. At ten years, the combined control strategies surpassed the benefit of either intervention when implemented individually over the same time period. For the second batch, greater Naloxone availability was tested in combination with drug reformulation. This combination was one of the most effective batches of the five tested after five years, even though both control strategies when tested individually actually increased the number of heroin abusers in the simulation when compared to baseline model results. However, after ten years the heroin abuser population did eventually increase by 0.45% from the baseline model values. The effect on heroin overdose deaths improved only slightly after five years, while the remaining metrics showed strong improvement.

The third batch combined expanded Naloxone availability and MAT, motivated by the question of whether the benefits of MAT could compensate for wider Naloxone availability slightly increasing the number of opioid abusers in the individual simulations prior. This was indeed the case, with the strengths of either strategy complementing the other one nicely. After ten years, model results improved in every category. For the fourth batch, PMP was tested with drug reformulation. Although the best decrease in the number of individuals abusing pharmaceutical opioids was obtained with this combination of control methods, the number of heroin abusers and heroin overdose deaths

increased after five years. This was not the case after ten years, however, indicative of a longer time required for the benefits to manifest in the system. The final batch combined three methods: expanded Naloxone availability, increased treatment accessibility, and drug reformulation. After five years, results were the best of all the batches tested. Pharmaceutical opioid overdose deaths decreased by nearly 10%, while both pharmaceutical opioid abusers and heroin overdose deaths decreased by over 5%. At ten years these numbers were even larger.

CHAPTER V

RESULTS AND DISCUSSION

Results are first presented for the parametric analysis, including parametric uncertainty and fitting. Following this, results are presented together for the local and global sensitivity analyses performed, as well as for the stochastic simulation results of the previous subsection.

Parametric uncertainty and fitting revealed that the contribution of the nonlinear transmission term β was less important than the linear transition rate γ in the transition of individuals from abusing pharmaceutical opioids to abusing heroin. Furthermore, parameter fitting in particular suggested that interaction terms accounting for movement into A_H was not significant. We speculate this is a result of Maine's predominantly rural population. That being said, interventions aimed at reducing the number of individuals abusing heroin were found to be more successful when they intervened when individuals first started abusing pharmaceutical opioids. This is because illicit community sources of recruitment into A_H did not contribute as strongly as did natural progression into initiation from misusing/abusing pharmaceutical opioids.

Local sensitivity analysis of the state variable A_P indicates that the treatment rate of heroin abusers (η_H) was the most influential. Admittedly, this probably has more to do with our assumptions of relapse and re-entry into either A_P or A_H, so we instead focus on the rate of addiction from opioid use (η_P), the proportion of Mainers with an opioid prescription (ρ), and the relapse probability (δ), as these parameters were also found to be very influential. It should come as no surprise that these parame-

ters were found to be the most influential in regards to local perturbations. What is surprising, however, is that these parameters were found to be more influential than the treatment rate of pharmaceutical opioid abusers (η_P), albeit only slightly so. This suggests that interventions are more effective in reducing the number of individuals in A_P when aimed at prevention rather than treatment. This was reflected in stochastic simulation results as well, as interventions targeting the aforementioned parameters (PMP, MAT, and drug reformulation) were the most successful in reducing the number of people abusing pharmaceutical opioids, both in the short term (five years) and the long term (ten years). Globally speaking, the sensitivity analysis found ε_P and ρ as the most significant in controlling A_P. The parameter η_P was found to be only slightly less influential, agreeing with the sensitivity analysis. In contrast with the local sensitivity analysis, δ was not found to be as significant when tested within its parameter range. This is most likely because even within its tested range, δ is still rather high, so control methods targeting other underlying dynamics find more success overall. We may conclude that in order to most significantly reduce the number of pharmaceutical opioid abusers, control strategies should reduce the number of prescriptions for opioids in Maine, and reduce the rate at which individuals develop an addiction to abusing pharmaceutical opioids.

For heroin abusers, local sensitivity analysis determined that the rate at which individuals relapse was the most influential parameter, and by a sizeable margin. This suggests that the role of sustained relapse is a significant contributor, especially when combined with the fact that individuals who relapse back into A_P can still progress to heroin use. Thus, relapse plays a significant part in the overall size of the heroin abuser population. The time scale should be noted here. At five years, the sensitivity of A_H to δ is comparable to that of η_H (see corresponding plots in Figure 10). At ten years, on the other hand, the sensitivity to η_H seems to flatten while the sensitivity to δ continues on in an almost linear trend. The global sensitivity analysis agrees with this phenomenon:

in the short-term, η_H is more influential in controlling A_H, while δ is more influential in the long-term. The stochastic simulations in the previous subsection suggest that increasing treatment accessibility is more effective at reducing the size of A_H both in the short- and long-term than MAT, which reduces the relapse probability. However, increasing treatment accessibility increases η_H *and* η_P. We conclude that, in order to reduce the number of heroin abusers, short-term strategies should emphasize treatment while longer term strategies should target reducing relapse among patients.

Finally, we addressed the question of most effectively reducing *all* opioid abusers in the system - both pharmaceutical opioids and heroin. Global sensitivity analysis results found that ε_P and ρ were the most influential parameters overall, both at five and ten years into the future. This is echoed by the stochastic simulations, which found that drug reformulation (which reduced ρ and ε_P) led to the greatest reduction in abusers in either category at either time tested. In this regard, the most successful combination of strategies was with expanded Naloxone availability and drug reformulation, but only at five years. Ten year results favored the combination of expanded Naloxone availability, increased treatment accessibility, and drug reformulation as the most effective in reducing overall opioid abuser numbers. It is no coincidence that the control strategies the most effective at reducing overall opioid abuser numbers are also the most effective in reducing the number of pharmaceutical opioid abusers alone. This is because our model formulation assumes that heroin abusers began abusing pharmaceutical opioids. Parameter fitting ruled out any contributions of recruitment from the susceptible class, and research in this area also suggests that a large majority of heroin abusers began their drug abuse with pharmaceutical opioids [39, 40, 59]. Our work above indicates that the brunt of Maine's heroin problem is almost entirely explained by pharmaceutical opioid abuse, and a solution to the latter by our estimates would reduce the problem of heroin abuse significantly.

We now move to the discussion of this study, including limitations and future work.

The most obvious drawback to our work is limited data, which affected everything from parameter estimations to model calibration. First and foremost, finer data (i.e. monthly data versus the yearly data that was used) would improve the accuracy of our model forecasts and parameter fitting. Even if the yearly data scale is to be kept, the release of new data in the years to come will help to refine the accuracy of our analysis. Data scarcity affected the estimation of certain parameters, most notably the proportion of Mainers with an opioid prescription, ρ, and the treatment rate of abusers of pharmaceutical opioids, η_P. These parameters can be updated when access to the proper data is provided, but this was not possible at the time of writing due to limitations of time and money. Some data sources that could be used in future work include the Maine Prescription Monitoring Program (PMP), the Web Infrastructure for Treatment Services (WITS), and the Treatment Data System (TDS). The global sensitivity analysis performed was intended in part to compensate for the potential error in estimating the aforementioned parameters.

Regarding the NSDUH data presented in the corresponding subsection in Chapter III, annual state prevalence estimates do not specify overlap, which is a potential problem since opioid abuse comorbidity is not uncommon [82]. Data values were thus taken at face value, but a more careful analysis could be performed that incorporates various proportions of overlap in the future. Beyond this, future work could include a broader nonpharmaceutical opioid compartment as data become available regarding abuse patterns of illicit opioids besides heroin, most notably fentanyl. Nonetheless, we hope that the above document serves as a template for future opioid epidemic models useful for informing public policy.

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